In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: October 8, 2021

TIMOTHY KOLLER,	*	PUBLISHED
Petitioner,	*	No. 16-439V
v.	*	Special Master Gowen
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Entitlement; Pneumococcal Conjugate Vaccination ("Prevnar"); Guillain-Barré Syndrome ("GBS").
Respondent.	*	

Maximillian J. Muller, Muller Brazil, LLP, Dresher, PA, for petitioner.
Dhairya D. Jani, U.S. Department of Justice, Washington, D.C., for respondent.

RULING ON ENTITLEMENT[1]

On April 6, 2016, Timothy Koller ("petitioner") filed a petition for compensation under the National Vaccine Injury Compensation Program.[2] Petitioner alleges that the pneumococcal conjugate vaccination ("Prevnar 13" or "Prevnar") he received on May 13, 2015 was the cause-in-fact of his Guillain-Barré Syndrome ("GBS"). Petition at Preamble (ECF No. 1); Petitioner's Post-Hearing Brief at Preamble (ECF No. 65). Based on a full review of the evidence and testimony, I find that petitioner is entitled to compensation.[3]

[1] In accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 (2012), because this opinion contains a reasoned explanation for the action in this case, **this opinion will be posted on the website of the United States Court of Federal Claims**. This means the opinion will be available to anyone with access to the internet. As provided by 42 U.S.C. § 300aa-12(d)(4)B), however, the parties may object to the published Decision's inclusion of certain kinds of confidential information. Specifically, under Vaccine Rule 18(b), each party has 14 days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). **If neither party files a motion for redaction within 14 days, the entire opinion will be posted on the website and available to the public in its current form.** *Id.*

[2] The National Vaccine Injury Compensation Program is set forth in 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 to 34 (2012) (hereinafter "Vaccine Act" or "the Act"). Hereinafter, individual section references will be to 42 U.S.C. § 300aa of the Act.

[3] Pursuant to Section 300aa-13(a)(1), in order to reach my conclusion, I have considered the entire record including all of the medical records, statements, expert reports, and medical literature submitted by the parties. This opinion discusses the elements of the record I found most relevant to the outcome.

I. PROCEDURAL HISTORY

Petitioner filed his petition on April 6, 2016, alleging that the Prevnar 13 vaccination he received on May 13, 2015 caused him to suffer GBS. Petition at Preamble. The petition was accompanied by medical records. Petitioner's Exhibits ("Pet. Ex.") 1-7. After an initial status conference, the respondent filed a status report stating that the record is substantially complete, and that the respondent intends to defend against the claim. Respondent ("Resp.") Status Report ("Rept.") (ECF No. 13).

On September 30, 2016, petitioner filed an expert report by Lawrence Steinman, M.D.,[4] Pet. Ex. 8 (ECF No. 16). Dr. Steinman opined that the Prevnar 13 vaccine caused petitioner's GBS, proposing a medical theory of causation of molecular mimicry. *Id.* at 9. Dr. Steinman also opined that petitioner's development of GBS was within a medically appropriate temporal timeframe. *Id.* at 8.

On March 8, 2017, respondent filed his Rule 4(c) Report, recommending against compensation in this case. Resp. Rept. at 8. Specifically, respondent stated that petitioner's medical theory of causation was not credible, none of petitioner's doctors attributed his GBS to the Prevnar vaccine, and that a temporal association alone is insufficient to establish entitlement. *Id.* at 6-8. The same day, respondent filed an expert report from Thomas P. Leist, M.D., PhD.[5] Resp. Ex. A (ECF No. 27).

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[4] Dr. Lawrence Steinman is a Professor of Neurological Sciences, Neurology and Pediatrics at Stanford University Medical Center. Pet. Ex. 8; Pet. Ex. 10, Tab 3. Dr. Steinman received his undergraduate degree from Dartmouth College in 1968 and graduated from Harvard University Medical School in 1973. Pet. Ex. 10, Tab 3 at 1. He had his post-graduate training at Stanford University Hospital and completed a Pediatric and Adult Neurology residency in 1980. Dr. Steinman is board certified in Psychiatry and Neurology. *Id.* at 2. Dr. Steinman has cared for adult and pediatric patients with various forms of inflammatory neuropathy, including, GBS, transverse myelitis, acute disseminated encephalomyelitis, neuromyelitis optic and multiple sclerosis. Pet. Ex. 8 at 1. Additionally, Dr. Steinman has served on multiple National Institutes of Health's ("NIH") expert panels pertaining to vaccination, including the Advisory Committee on Pertussis Immunization and the Immunological Sciences Study Section. *Id.* at 1. Dr. Steinman was awarded the Charcot Prize for Lifetime Achievement from the International Federation of MS Societies for his work in multiple sclerosis research. *Id.* at 2. In 2015, Dr. Steinman was elected to the National Academy of Science. *Id.* Dr. Steinman has authored or co-authored over 100 medical articles. Pet. Ex. 10, Tab 3 at 5-43. Additionally, Dr. Steinman has testified before the Vaccine Court as an expert in neurology and immunology. As such, I admitted Dr. Steinman as an expert in neurology and immunology, with a specialty in neuroimmunology in this case. *See* Tr. 10.

[5] Dr. Thomas Leist is a neurologist licensed to practice medicine in Pennsylvania, Maryland and New York. Resp. Ex. B at 1. He received his undergraduate degree from University of Zurich in Switzerland in 1982. *Id.* Dr. Leist received his PhD in biochemistry from the University of Zurich in 1985. *Id.* Dr. Leist received his medical degree from the University of Miami in Miami, Florida in 1993. He had his residency in Neurology at the Cornell Medical Center/Sloan Kettering Memorial Cancer Center in New York. From 1997-2000 Dr. Leist was a clinical senior staff associate at NINDS at the NIH in Bethesda, MD. Dr. Leist is board certified in Psychiatry and Neurology and neuroimmunology. *Id.*; Tr. 66. Dr. Leist is currently a Professor of Neurology at the Thomas Jefferson University and is the Chief, Division Clinical Neuroimmunology Director at the Comprehensive Multiple Sclerosis Center. *Id.* In this role, Dr. Leist treats patients with multiple sclerosis, neuromyelitis optic, and GBS. Tr. 67. Dr. Leist also serves on the Clinical Advisory Committee at the National Multiple Sclerosis Society. *Id.* at 3. Additionally, he has authored or co-authored over 50 medical articles that were published in peer-reviewed medical journals and

On April 25, 2017, I held a Rule 5 Status Conference, where I indicated that it appeared that petitioner had a Miller-Fisher variant of GBS and that the timing in this case appeared to be medically appropriate. Rule 5 Order (ECF No. 28). I requested that the parties file supplemental expert reports and to answer specific questions related to the components of the Prevnar 13 vaccine and how those components can cross-react with myelin. *Id.* On June 14, 2017, petitioner filed a supplemental expert report from Dr. Steinman. Pet. Ex. 10. Respondent filed a supplemental report by Dr. Leist on October 10, 2017. Resp. Ex. C (ECF No. 35).

On October 31, 2017, I held another status conference in the case, where respondent remained committed to a litigative track. Order (ECF No. 36). I held another status conference on September 13, 2019 and issued a pre-hearing order on October 15, 2019, outlining a schedule for pre-hearing submissions and set a date and location for an entitlement hearing. Pre-Hearing Order (ECF No. 41).

On January 21, 2020, the parties filed a joint submission, explaining that they did not dispute that petitioner suffered from the Miller-Fisher variant of GBS and that the issues that remained to be resolved were: (1) whether the Prevnar-13 vaccination can cause the Miller-Fisher variant of GBS; and (2) whether petitioner's Miller-Fisher variant of GBS was caused by his receipt of a Prevnar-13 vaccination on May 13, 2015. Joint Pre-Hearing Submission (ECF No. 51). Both parties filed pre-hearing briefs. *See* Pet. Pre-Hearing Brief (ECF No. 47); Resp. Pre-Hearing Brief (ECF No. 48).

Observing that some of the language included in petitioner's expert reports was confusing, I held another status conference on February 4, 2020 explaining that one of the key issues that the experts needed to address was whether phospholipids are present in the Prevnar-13 vaccine and whether the phospholipid is essential to achieving the immunogenicity desired. Scheduling Order (ECF No. 56).

An entitlement hearing was held on February 6, 2020, where Dr. Steinman testified on behalf of petitioner and Dr. Leist testified on behalf of respondent. At respondent's request, the parties submitted post-hearing expert reports to address issues raised because of Dr. Steinman clarifying his theory during the hearing. Dr. Leist filed his response to the trial testimony with an explanation of terminology and his basis of his disagreement as to causation and Dr. Steinman provided an extensive report detailing his theory in response. *See* Resp. Ex. E; Pet. Ex. 16.

Petitioner filed a post-hearing brief on October 30, 2020. Pet. Post-Hearing Brief (ECF No. 65). On March 4, 2021, respondent filed a post-hearing brief. Resp. Post-Hearing Brief (ECF No. 68). Petitioner did not file a reply.

This matter is now ripe for adjudication.

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participated as a researcher in multiple clinical trials. *Id.* at 11. Dr. Leist has testified before the Vaccine Court as an expert in neuroimmunology and I admitted him as such for this case. Tr. 69

II. FACTUAL HISTORY

On May 13, 2015, petitioner, a 65-year-old male, presented to Dr. Dallas Bogner for an initial Medicare examination. Pet. Ex. 1 at 2. His physical exam was normal, and he was counseled to exercise for 150 minutes per week and a prostate cancer screening was recommended. *Id.*at 6. At this appointment, the Pneumococcal 13-Valent Conjugate vaccine was administered to the petitioner. *Id.* at 8.

On May 27, 2015, petitioner presented to the Theda Clark Emergency Department complaining of left sided facial weakness. Pet. Ex. 6 at 1. Petitioner explained that two days prior, he had a headache, body aches and difficulty sleeping. *Id.* That morning, petitioner developed left sided facial droop while brushing his teeth. *Id.* He denied fever, chills, nausea, vomiting, diarrhea, abdominal pain, double vision, generalized weakness or paresthesias. *Id.* Neurologist, Dr. Thomas G. Mattio, examined petitioner in the emergency department. *Id.* at 9. During the consultation, petitioner also explained he had a loss of taste the night before. *Id.* The physical exam revealed petitioner had left eye closure weakness and left facial weakness "with decreased wrinkling of the left forehead." *Id.* at 10. Dr. Mattio assessed petitioner with "very early Bell's palsy," and recommended a course of steroids. *Id.* Dr. Mattio directed that if petitioner developed any other weakness, he should return to the emergency department. *Id.* Petitioner was discharged to home.

On May 28, 2015, the following day, petitioner returned to the Theda Clark Emergency Department, this time indicating that he had developed right side weakness as well. Pet. Ex. 6 at 11. Petitioner described a metal taste in his mouth and worsening word pronunciation. *Id.* An MRI of petitioner's head was ordered. *Id.* Petitioner was again discharged with Bell's palsy and it was recommended he continue with his steroid course and follow-up with a neurologist. *Id.* at 16.

On June 1, 2015, petitioner returned to the Theda Clark Emergency Department, with a complaint of difficulty walking. Pet. Ex. 6 at 19. Petitioner explained that he was taking prednisone after being diagnosed with Bell's palsy. *Id.* Since his last emergency department visit on May 28, 2015, petitioner had developed low back tightness with radiation down both buttocks and leg weakness to the point where he needed to utilize a walker to ambulate. *Id.* Petitioner explained that he had received the Prevnar vaccine on May 13 and was "wondering if the symptoms may be related to [the vaccination]." *Id.* A physical exam revealed petitioner had absent patellar and Achilles reflexes bilaterally and a cranial nerve deficit was present. *Id.* at 22. It was noted that petitioner had a "waddling gait", and petitioner could not go from squatting to standing due to weakness. *Id.* Petitioner was admitted to the hospital. *Id.* At the time of his admission there was a "high concern for a demyelinating condition," and his differential diagnosis included, "atypical Guillain-Barre syndrome, inflammatory demyelinating polyneuropathy, myositis…." *Id.* at 23. An MRI of petitioner's thoracic and lumbar spine revealed an abnormal enhancement of the ventral nerve roots at the lumbosacral plexus typical of acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barre syndrome). Pet. Ex. 7 at 134.

Petitioner was assessed by neurologist Dr. Steven W. Huder upon admission. Pet. Ex. 6 at 26. He reviewed petitioner's MRI of the thoracic and lumbar spine which revealed enhancement of the ventral nerve roots of the lumbosacral plexus consistent with demyelination. *Id.* He observed that petitioner was areflexic diffusely and he could not elicit plantar responses. *Id.* at 28. Dr. Huder diagnosed petitioner with, "probable Guillain-Barre syndrome with bilateral facial nerve involvement as well as lower extremity involvement with the lumbosacral plexus." *Id.* Dr. Huder ordered a lumbar puncture. *Id.* The lumbar puncture revealed an elevated CSF protein of 182 and WBC of 2. *Id.* at 29. As a result, Dr. Huder ordered that petitioner begin plasmapheresis. *Id.* at 31.

Petitioner had a consult with nephrologist, Dr. Riess Sagers. *Id.* at 31. Dr. Sagers noted that petitioner was admitted for progressive lower extremity weakness accompanied by numbness and pain. *Id.* Dr. Sagers also wrote, "Lumbar puncture done. Felt to have Guillain-Barré syndrome following vaccination." *Id.*

On June 3, 2015, following plasmapheresis, petitioner reported increased numbness in his feet and that his legs were getting weaker. Pet. Ex. 6 at 58. Additionally, his fingers were getting numb, and his facial weakness was unchanged. *Id.* The following day, on June 4, 2015, petitioner had new horizontal diplopia, worse in the right than left, left hand weakness and numbness in his fingertips. *Id.* at 68. This was the third day of the plasmapheresis. Dr. Hudson noted that petitioner's diagnosis was, "Miller-Fisher variant Guillain-Barre syndrome, after vaccination. Still with subtle daily worsening, but autonomically fairly stable, swallow and breathing preserved thus far...continue plasma exchange for at least 5 days consecutively." *Id.* at 69-70.

Petitioner received an additional five-day course of plasmapheresis. Pet. Ex. 6 at 102-03. On June 8, 2015, petitioner was discharged to inpatient rehabilitation, despite continuing plasmapheresis treatment. *Id.* Petitioner was seen by Dr. Scott G. Powley the same day and he noted that petitioner was, "A 65-year-old right-handed male with onset of Miller Fisher variant Guillain-Barré syndrome, likely due to pneumococcal vaccine he received a week to a week and half earlier. He has had improvement with plasmapheresis, but still has substantial deficits." *Id.* at 107. Dr. Powley observed that petitioner is a very good candidate for inpatient rehab and petitioner is extremely motivated. *Id.*

Petitioner was discharged from the Theda Clark Medical Center to home with ongoing outpatient physical therapy and occupational therapy. Pet. Ex. 6 at 150-52. Petitioner's discharge diagnosis was Guillain-Barré syndrome (Miller-Fisher variant). *Id.* at 149. Upon discharge, petitioner was utilizing a four-wheeled rollator, and continued to have aching discomfort. *Id.* at 152.

On July 3, 2015, petitioner had a hospital follow-up appointment with his primary care physician, Dr. Bogner. Pet. Ex. 3 at 6. It was recorded that petitioner's diagnosis was, "Guillain-Barré syndrome following vaccination; leg weakness, bilateral; and neuropathic pain." *Id.* Dr. Bogner noted that petitioner was "making an impressive improvement from Guillain Barré after Prevnar vaccination. He feels daily improvement, with still symptoms of diplopia,

neuropathic back pain, facial paralysis, leg weakness." *Id.* at 10. Dr. Bogner also indicated that he would "report vaccine incident." *Id.*

On August 3, 2015, petitioner had a neurology follow-up appointment with Dr. Gizell Larson. Pet. Ex. 2 at 13. At this appointment, Dr. Larson wrote, "[Petitioner] was hospitalized for a long time at Theda Clark with Miller Fisher variant of Guillain-Barré syndrome that developed within 1 week of receiving a pneumococcal vaccine." *Id.* Dr. Larson stated that petitioner had just recently started to move his toes, but still has balance and strength issues, along with loss of sensation on his face and lower distal extremities. *Id.* Dr. Larson also wrote, "Patient and wife reported the event to the vaccine reporting office. *I do believe that this is, indeed, due to the pneumococcal vaccine." Id.* (emphasis added). Petitioner's diagnosis was, "Recovering Miller Fisher-variant Guillain-Barre syndrome status post pneumococcal vaccine, residual bifacial palsy with concern about corneal desiccation/ulceration." *Id.* at 14.

Petitioner had a follow-up appointment with Dr. Scott Powley at Thedacare Orthopedics Plus Center for Rehabilitation Services on August 20, 2015. Pet. Ex. 4 at 3. Dr. Powely noted that petitioner's symptoms came on shortly after receiving the pneumonia vaccine and he was hospitalized at Theda Clark. *Id.* Petitioner reported that physical therapy was improving his gait and movement and that he was doing water exercises on his own. *Id.* Dr. Powley noted that the right-side of petitioner's face had regained strength, but the left side was still plegic. *Id.* Additionally, petitioner reported ongoing neuropathic pain in his feet and hands but was gradually decreasing his dose of gabapentin. *Id.* After a physical exam, Dr. Powley's impression was that petitioner had Miller Fisher variant of GBS "shortly after receiving the pneumonia vaccine," and that petitioner had improved since hospitalization, but not yet back to baseline. *Id.* at 4.

On October 20, 2015, petitioner had another appointment with Dr. Powley. Pet. Ex. 4 at 1. Dr. Powley noted that petitioner continued to show slow improvement since the previous appointment, and he had gained more motion in his face on the right side. *Id.* Petitioner explained that he was still having abnormal sensation in both feet, especially in the evening. *Id.* Dr. Powley observed that petitioner was still unable to close both his eyes totally and had primarily left facial paralysis, despite improvements. *Id.* at 2. Dr. Powley indicated that petitioner could follow-up as needed. *Id.*

On November 10, 2015, petitioner had a follow-up appointment with Dr. Gizell Larson. Pet. Ex. 2 at 11. Dr. Larson explained, "I saw [petitioner] for follow-up for Miller Fisher variant of Guillain-Barré due to pneumococcal vaccine. His syndrome was quite severe, requiring multiple rounds of IVIG." *Id.* Dr. Larson explained that petitioner's primary residual symptom is bifacial palsy and that petitioner had difficulty closing his eyes. *Id.* Additionally, petitioner's lower facial paralysis affects his ability to speak and that he does not have normal facial expression. *Id.* Dr. Larson stated that petitioner could not purse his lips, making drinking from a glass or straw difficult and he had residual fine motor control issues. *Id.* Dr. Larson recommended that petitioner avoid immunizations and continue to avoid alcohol. *Id.* Dr. Larson's impression was, "Continuing recovery status post severe postvaccination Miller Fisher variant Guillain-Barre." *Id.* at 12.

On September 20, 2017, petitioner had an annual wellness exam. Pet. Ex. 11 at 26-34. The physical exam revealed that petitioner had hypoactive reflexes in his knees and ankles bilaterally. *Id.* at 33. Relevant to this case, petitioner was diagnosed with "Guillain-Barré syndrome," and it was noted that petitioner, "has some residual, nerve issues, responsiveness." *Id.* at 34. Petitioner also reported that, "things feel lazy, he can't read as fast or follow tennis balls as close," and he had dexterity issues, along with numbness in his feet. *Id.* In July 2019, during another annual wellness exam, petitioner reported that he was having neuropathy in his feet and face. *Id.* at 15. He also demonstrated reduced reflexes in his knees and ankles bilaterally during the physical exam. *Id.* at 14. Petitioner was again diagnosed with GBS. *Id.* at 15.

On July 29, 2016, petitioner established care with Advance Nurse Practitioner Brenda Brusky. Pet. Ex. 11 at 51. It was noted in his medical history that he had the Miller Fisher variant of GBS due to "immunization of Prevnar 13," and he was hospitalized for months. *Id.* Petitioner reported that he felt that he was "regressing," and he was getting headaches and dizziness. *Id.* Petitioner indicated he had gotten new glasses and started getting headaches behind his left eye. *Id.* Petitioner was assessed with headaches, dizziness and history of GBS. *Id.* at 54.

At an annual physical in 2019, noted that petitioner had GBS four years ago and was "doing well," although he had some residual neuropathy in feet and face. Pet. Ex. 11 at 14-15. These were the latest records filed in the case.

III. LEGAL STANDARD

The Vaccine Act was established to compensate vaccine-related injuries and deaths. § 10(a). "Congress designed the Vaccine Program to supplement the state law civil tort system as a simple, fair and expeditious means for compensating vaccine-related injured persons. The Program was established to award 'vaccine-injured persons quickly, easily, and with certainty and generosity.'" *Rooks v. Sec'y of Health & Hum. Servs.,* 35 Fed. Cl. 1, 7 (1996) (quoting H.R. Rep. No. 908 at 3, reprinted in 1986 U.S.C.C.A.N. at 6287, 6344).

Petitioner's burden of proof is by a preponderance of the evidence. § 13(a)(1). The preponderance standard requires a petitioner to demonstrate that it is more likely than not that the vaccine at issue caused the injury. *Moberly v. Sec'y of Health & Hum. Servs.*, 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010). Proof of medical certainty is not required. *Bunting v. Sec'y of Health & Hum. Servs.,* 931 F.2d 867, 873 (Fed. Cir. 1991). In particular, petitioner must prove that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly*, 592 F.3d at 1321 (quoting *Shyface v. Sec'y of Health & Hum. Servs*., 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)); see also *Pafford v. Sec'y of Health & Hum. Servs.,* 451 F.3d 1352, 1355 (Fed. Cir. 2006). A petitioner who satisfies this burden is entitled to compensation unless respondent can prove, by a preponderance of the evidence, that the vaccinee's injury is due to factors unrelated to the administration of the vaccine." § 13(a)(1)(B).

To receive compensation through the Program, petitioner must prove either (1) that she suffered a "Table Injury"—i.e., an injury listed on the Vaccine Injury Table—corresponding to a vaccine that she received, or (2) that he suffered an injury that was actually caused by a

vaccination. See §§ 11(c)(1), 13(a)(1)(A); *Capizzano v. Sec'y of Health & Hum. Servs.,* 440 F.3d 1317, 1319-20 (Fed. Cir. 2006). Because petitioner does not allege that he suffered a Table Injury, he must prove that a vaccine he received caused her injury. To do so, he must establish, by preponderant evidence: (1) a medical theory causally connecting the vaccine and his injury ("*Althen* Prong One"); (2) a logical sequence of cause and effect showing that the vaccine was the reason for her injury ("*Althen* Prong Two"); and (3) a showing of a proximate temporal relationship between the vaccine and her injury ("*Althen* Prong Three"). § 13(a)(1); *Althen*, 418 F.3d at 1278.

The causation theory must relate to the injury alleged. The petitioner must provide a sound and reliable medical or scientific explanation that pertains specifically to this case, although the explanation need only be "legally probable, not medically or scientifically certain." *Knudsen v. Sec'y of Health & Hum. Servs*., 35 F.3d 543, 548-49 (Fed. Cir. 1994). Recently, in *Kottenstette,* the Federal Circuit reiterated that proof of causation does not "require identification and proof of specific biological mechanisms[.]" *Kottenstette v. Sec'y of Health & Hum. Servs.*, --Fed.Appx.—(Fed. Cir. June 15, 2021) (citing *Knudsen v. Sec'y of Health & Hum. Servs.*, 35 F.3d 543, 549 (Fed. Cir. 1994). Causation "can be found in vaccine cases….without detailed medical and scientific exposition of the biological mechanisms." *Knudsen*, 35 F.3d 543, 548-49 (Fed. Cir. 1994). It is not necessary for a petitioner to point to conclusive evidence in the medical literature linking a vaccine to the petitioner's injury, as long as the petitioner can show by a preponderance of evidence that there is a causal relationship between the vaccine and the injury, whatever the details of the mechanism may be. *Moberly v. Sec'y of Health & Hum. Servs.*, 592 F.3d 1315, 1325 (Fed. Cir. 2010).

Petitioner cannot establish entitlement to compensation based solely on his assertions; rather, a vaccine claim must be supported either by medical records or by the opinion of a medical doctor. § 13(a)(1). In determining whether petitioner is entitled to compensation, the special master shall consider all material in the record, including "any . . . conclusion, [or] medical judgment . . . which is contained in the record regarding . . . causation." § 13(b)(1)(A). The undersigned must weigh the submitted evidence and the testimony of the parties' proffered experts and rule in petitioner's favor when the evidence weighs in his favor. *See Moberly*, 592 F.3d at 1325-26 ("Finders of fact are entitled—indeed, expected—to make determinations as to the reliability of the evidence presented to them and, if appropriate, as to the credibility of the persons presenting that evidence."); *Althen*, 418 F.3d at 1280 (noting that "close calls" are resolved in petitioner's favor).

In Vaccine Act cases, expert testimony may be evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharm., Inc.*, 509 U.S. 579, 594-96 (1993); *see also Cedillo*, 617 F.3d at 1339 (citing *Terran v. Sec'y of Health & Hum. Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999). In Vaccine Program cases, the *Daubert* analysis has been used in the weighing of the scientific evidence actually proffered and heard rather than as a tool for the pre-trial exclusion of expert testimony. *Davis v. Sec'y of Health & Hum. Servs.*, 94 Fed. Cl. 53, 66–67 (Fed. Cl. 2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"), *aff'd*, 420 F. App'x 923 (Fed. Cir. 2011). The flexible use of the *Daubert* factors to determine the persuasiveness and/or reliability of expert testimony in

Vaccine Program cases has routinely been upheld. *See, e.g.*, *Snyder v. Sec'y of Health & Hum. Servs.*, 88 Fed. Cl. 706, 742–45 (2009).

Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Hum. Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe v. Sec'y of Health & Hum. Servs.*, 219 F.3d 1357, 1362 (Fed. Cir. 2000)). However, 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*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 146 (1997)). Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Moberly*, 592 F.3d at 1325–26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Hum. Servs.*, 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act").

Close calls regarding causation must be resolved in favor of the petitioner. *Althen*, 418 F.3d at 1280 (holding that Congress created a system in which "close calls regarding causation are resolved in favor of injured claimants"); *Knudsen*, 35 F.3d at 551 ("If the evidence (on alternative cause) is seen in equipoise, then the government has failed in its burden of persuasion and compensation must be awarded.").

IV. Analysis

A. *Althen* prong one

Under *Althen* prong one, the causation theory must relate to the injury alleged. The theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen*, 35 F.3d at 548. It must only be "legally probable, not medically or scientifically certain." *Id.* at 549. However, the theory still must be based on a "sound and reliable medical or scientific explanation." *Id.* at 548. The Federal Circuit explained in *Althen* that "while [that petitioner's claim] involves the possible link between [tetanus toxoid] vaccination and central nervous system injury, *a sequence hitherto unproven in medicine*, the 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 (emphasis added).

1. Dr. Steinman's opinion on medical theory of causation

Dr. Steinman explained that Guillain-Barré syndrome is "an inflammatory attack by the immune system on the peripheral nerves." Tr. 15. According to the *Gilburd et al*. article cited by Dr. Steinman, GBS is "associated with an inflammatory demyelination of peripheral nerves."

Pet. Ex. 10, Tab 14 at 1.[6] The article explained that the demyelination in GBS is thought to be initiated by an autoimmune reaction. *Id.* Dr. Steinman stated that, "In the case of the Miller Fisher variant of GBS, it involves the peripheral nerves in the brain stem, the facial nerves, as well as the nerves that come off the spinal cord that innervate the arms and legs." *Id.* Dr. Steinman explained that GBS can be caused by viral or bacterial infections. Tr. 16. Further, he testified that the "strongly held belief" based on a wide array of medical literature, is that GBS is caused by the immune system attacking the peripheral nerves. Tr. 17. He noted that the *campylobacter jejuni* (*"c.jejuni"*) bacterial infections are known to precede GBS and explained, "[*c.jejuni*] has a certain sugar that is the same as the sugar in your peripheral nerve. And it's one of the classic examples that the Institute of Medicine and various papers use to exemplify this concept of molecular mimicry, something in that bacteria that's shared with something in the nerve." Tr. 18. There was no dispute that the petitioner was correctly diagnosed with the Miller Fisher variant of GBS or that GBS is generally considered a neuroinflammatory, autoimmune disease.

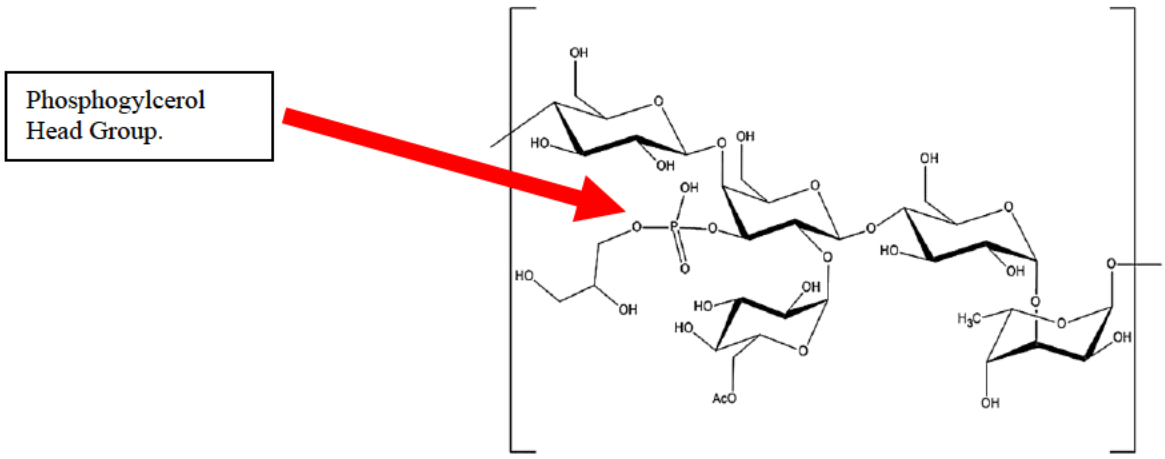
Dr. Steinman opined that petitioner's Miller Fisher variant of GBS was caused by the Prevnar 13 vaccine. Pet. Ex. 8; Pet. Ex. 10; Pet. Ex. 16. He proposed a theory of molecular mimicry between components of the Prevnar 13 vaccine and the myelin sheath of the peripheral nervous system which resulted in GBS. Pet. Ex. 8 at 7; Pet. Ex. 16 at 1; Pet. Post-Hearing Brief at 9. He stated that the Prevnar 13 vaccine includes a critical component known as a "phosphoglycerol," which is also a key component of phospholipids which make up 70% of the myelin. Pet. Ex. 16 at 1. The immune reaction to the phosphoglycerol in the vaccine can induce an attack on the phosphoglycerol attached to the phospholipids in the myelin. *Id.* He testified, "In this case, it's molecular mimicry to the phosphoglycerol that is connected to the polysaccharide structure of the vaccine that gives rise to GBS." Tr. 51. Dr. Steinman explained:

> The capsule in a polysaccharide vaccine is composed of sugars…and the package insert talks about the sterile suspension of saccharides of the capsular antigens that are linked individually to the diphtheria protein. But there is another component of those saccharides, of those sugars, that's actually central to my thesis. The immune system makes an immune response to the sugars, (in the vaccine) but only if, and that is really important, if the sugars are attached to something called phosphoglycerol. So, if you take away that linkage to the phosphoglycerol, …the vaccine is no longer immunogenic.

Tr. 19-20. Dr. Steinman explained that the Prevnar 13 vaccine contains *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 7F, 9V, 18C, 19A, 19F, and 23F as demonstrated by the package insert. Pet. Ex. 10 at 2. These individual polysaccharides are purified…. "and are chemically activated to make saccharides, which are directly conjugated by reductive amination to the protein carrier CRM197, to form the glycoconjugate. CRM197 is a nontoxic variant of diphtheria toxin…" Pet. Ex. 8; Tr. 18-20. He asserted that the polysaccharides contain a phosphoglycerol group. Tr. 32. In his supplemental report and post-hearing report, he pointed to the *Chang et al*. article to demonstrate that the chemical structure of *S. pneumoniae* serotype18C includes a phosphoglycerol side chain. Pet. Ex. 10 at 2; Pet. Ex. 16 at 9-10. During the hearing, he circled

[6] Gilburd, B. et al., *Autoantibodies to Phospholipids and Brain Extract in Patients with the Guillain-Barre Syndrome: Cross-Reactive or Pathogenic?* 16 Autoimmunity 23-27 (1993). [Pet. Ex. 10, Tab 14].

the phosphoglycerol group that is attached to the saccharide and re-created the diagram in his post-hearing report:



Resp. Ex. D[7]; Pet. Ex. 10 at 3; Court's Exhibit 2. Dr. Steinman testified that the molecule identified as 'P' on the diagram above, is the phosphate in the "phosphoglycerol group," in the vaccine which is attached to the capsular polysaccharides, which are represented by the thick black lines on the diagram. Tr. 32. He explained that the phosphate head group was connected to the sugars. Tr. 171. In Dr. Steinman's post-hearing report, he explained, "Phosphoglycerol is the scaffold for the fatty acids that adorn the arms of the three carbon molecules of phosphoglycerol. Phosphoglycerol is thus a building block of the vaccine and also of the phospholipid" in myelin. Pet. Ex. 16 at 2. Dr. Steinman stated that both the *Chang* article and the Prevnar patent application "reinforce" the importance of the glycerophosphate and that it is required for immunogenicity of the vaccine. Tr. 34-37.

Dr. Steinman's pre-trial reports used the term "phospholipid" when referring to components of both the vaccine and the myelin as opposed to specifically referring to the phosphoglycerol in the vaccine, which initially caused some confusion. At trial both doctors referred to a Wikipedia article entitled *Glycerophospholipid* to explain the distinction. Dr. Steinman explained that the article, titled *Glycerophospholipids,* which he referenced in his supplemental report, clarified that glycerophospholipids "are glycerol-based phospholipids." Tr. 26. The article explains that glycerol-based phospholipids are "the main component of biological membranes." Court's Exhibit 1; Pet. Ex. 10 at 6.[8] Further, the article explains that, "The alcohol is glycerol, to which two fatty acids and phosphoric acid are attached as esters. The two fatty acid chains attached to the molecule of glycerol are nonpolar…while the polar

[7] Chang, J., et al., *Relevance of O-acetyl and phosphoglycerol groups for the antigenicity of Streptococcus pneumoniae serotype 18C capsular polysaccharide*, 30 Vaccine 7090-7096 (2012). [Resp. Ex. D].

[8] *Glycerophospholipid,* Wikipedia the free encyclopedia, https://en.wikipedia.org/wiki/Glycerophospholipid [last accessed on September 27, 2021]. [Court's Exhibit 1].

heads which mainly consists of the phosphate group attach to the third carbon of the glycerol molecule is hydrophilic." *Id.*

Later in the hearing, Dr. Leist provided a detailed description of chemical structure of a phospholipid and the relationship between phospholipids and phosphoglycerol. As Dr. Leist explained, a phospholipid has two lipid tails and has a bridge which is the glycerol which is hydrophilic. The glycerol is often referred to as the polar head which sticks out from a lipid bilayer which is hydrophobic. He emphasized that the phosphoglycerol side chain is a *component* of a phospholipid but it is not by itself a phospholipid. The phospholipids are components of the membrane in myelin where two phospholipids or two layers of phospholipids butt each other with the hydrophilic surfaces on top of it to form a boundary between the inside and outside of the cells. Tr. 103 In Dr. Leist's post-hearing report, he stated, "A phosphoglycerol is composed of a glycerol and a phosphate unit, *and is a building block or component of a phospholipid…." Id.* at 2 (emphasis added).

Dr. Steinman agreed with Dr. Leist's explanation, stating that it was, "absolutely accurate," that a phosphoglycerol was a component of a phospholipid. Pet. Ex. 16 at 5; Tr. 166-67. He also acknowledged that the vaccine does not contain a phospholipid but asserted that the critical component in the cross reaction was the phosphoglycerol component of both the vaccine and the phospholipids in myelin.

Dr. Steinman observed that the *Chang* article studied the 18C serotype in the vaccine. The article explained that the 18C serotype "is composed of a repeating unit having a tetrasaccharide backbone with D-galactose highly branched by D-glucose and glycerol phosphate. Resp. Ex. D at 1. The authors noted that the repeating units have "two apparently labile components: glycerol-phosphate and an O-acetyl group (AcO)." *Id.* at 1. Additionally, the authors found that "glycerol-phosphate *must* be preserved for conserving adequate antigenicity of the 18C capsular polysaccharide." *Id.* at 1, 6 (emphasis added). Dr. Steinman testified that *Chang* shows that the glycerophosphate side chains need to be preserved to confer immunity. Tr. 37.

In further support of his theory, Dr. Steinman referenced the patent application for the Prevnar vaccine, which provided detailed information about the chemical composition of the vaccine. Pet. Ex. 12.[9] Dr. Steinman observed that the patent states, "An important consideration during conjugation is the development of conditions that permit the retention of potentially sensitive non-saccharide substituent function groups of the individual components, such as 0-Acetyl, phosphate or glycerol phosphate side chains that may form part of the saccharide epitope." *Id.* at 34; Tr. 37. Dr. Steinman interpreted the language in the vaccine patent to mean that that when the vaccine is made, "it's not only the sugar….but you must preserve these non-saccharide, non-sugar functional groups, such as…the glycerophosphate side chains that may form part of the saccharide epitope….And from *Chang*, if that is not preserved in the vaccine, there is no immunogenicity." Tr. 37.

[9] United States Patent, Patent No.: US 9,492,559 B2, *Immunogenic Compositions Comprising Conjugated Capsular Saccharide Antigens and Uses Thereof* (Nov. 15, 2016). [Pet. Ex. 12].

In his post-hearing report, Dr. Steinman noted that serotype 11A also contains a phosphoglycerol side chain. Pet. Ex. 16 at 15. The patent application provides, "The polysaccharide repeating unit of serotype 11A consists of a linear tetrasaccharide backbone (two galactopyranoses (Gal) and two glucopyranoses (Glc) and a pendent phosphoglycerol…..The polysaccharide is O-acetylated at multiple locations…." Pet. Ex. 12 at 24. Dr. Steinman explained that this language of the patent application means that the phosphoglycerol hangs from the pneumococcal polysaccharides in Prevnar 13. Pet. Ex. 16 at 14. He also observed that the patent application describes the existence of a phosphoglycerol side chain in Pneumococcal polysaccharide serotype 15B as well. Pet Ex. 16 at 10-11; Pet. Ex. 12 at 24. Dr. Steinman opined that to "a high degree of likelihood, it is true," that the other antigenic units that make up the Prevnar 13 vaccine also include the glycerophosphate side chain. Tr. 37.

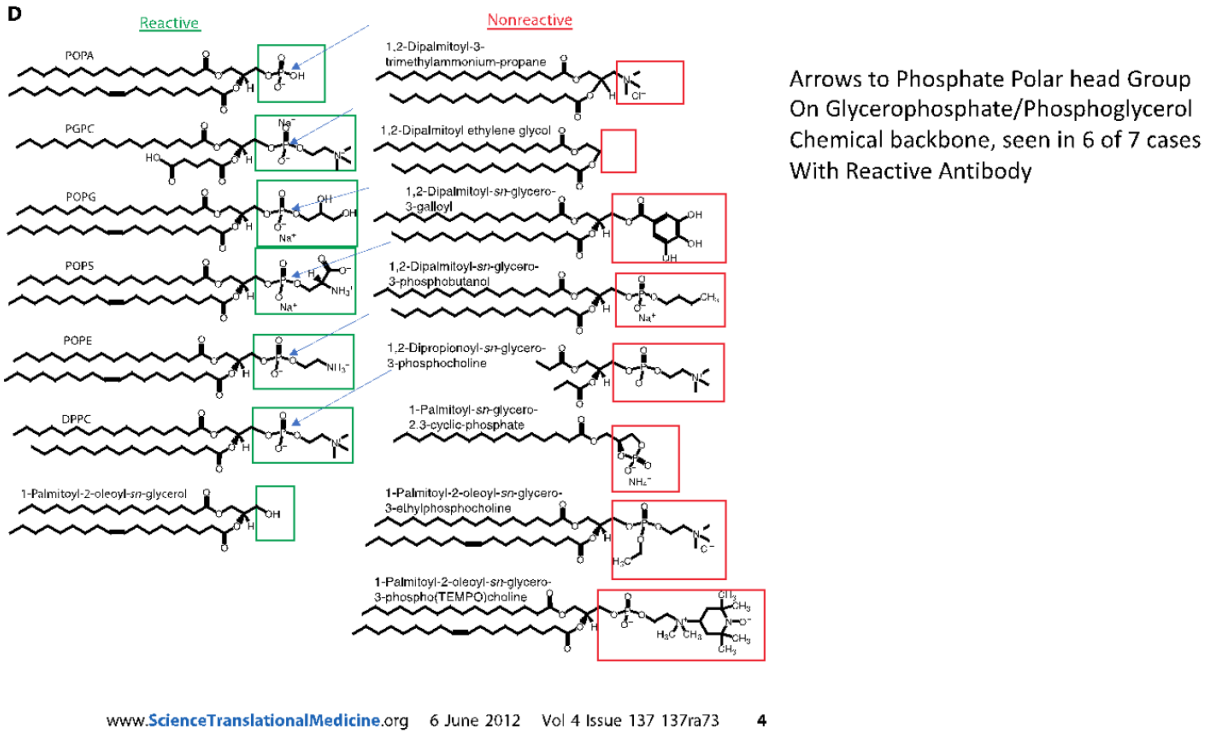
Dr. Steinman concluded that *Chang* and the patent application, taken together, demonstrate that the Prevnar 13 vaccine includes the phosphoglycerol side chains on different serotypes which need to be retained during the purification process to preserve immunogenicity of the vaccine. Tr. 37, 168-69. He said that if the phosphoglycerol side chain is not preserved in the manufacturing process, the vaccine would be "a dud." Tr. 168.

Dr. Steinman then explained that phospholipids are a component of the myelin sheath in humans, which are targets for antibodies in neuroinflammation. Pet. Ex. 8 at 6; Tr. 21. He testified that in GBS, the immune system attacks the myelin in peripheral nerves. Tr. 21. He cited to a study by *Ho et al.* to demonstrate that autoantibodies against phospholipids contribute to demyelination in multiple sclerosis ("MS") and that the autoantibodies target a phosphate group attached to the lipids. Pet. Ex. 10, Tab 8 at 1.[10] Dr. Steinman testified that *Ho* indicates that in MS, the immune system is not attacking the phospholipids in the myelin, but instead is attacking the phosphate headgroup, which is a component of the phospholipids in the myelin. Tr. 34. Based on *Ho*, he opined that the immune system attacks the phosphate headgroup on the phospholipids in the myelin in GBS, which is a close cousin of MS. Tr. 35.

In *Ho* the authors sought to determine whether lipids in the myelin sheath are targeted by autoimmune responses in MS and identified myelin lipids targeted by autoantibodies. Pet. Ex. 10, Tab 8 at 9. The authors investigated autoantibody targeting of lipids to determine the lipids' antigenicity with samples of CSF from 33 patients with MS. *Id.* at 1-3. Specifically, the authors explained, "We investigated autoantibody targeting of seven lipids that have a glycero-3-phosphocholine back bone in common with PGPC (an oxidized lipid), as well as targeting of other structurally similar lipids from the lipid array….such as those containing features in common with PGPC, including a phosphate head group with one or two nonpolar side chains." *Id.* at 3. The authors explained that they also sought to understand the "structural basis of the lipids' antigenicity," and they examined autoantibody reactivity to an additional 14 lipids that contain various head group and side-chain modifications of PGPC." *Id.* They found that "six of the seven *targeted* lipids had a phosphate group," and that "The other six lipids that were not targeted either lacked a phosphate group or contained a phosphate group connected to a bulky group, for example, a ring structure or a phosphate group linked to four carbons." *Id.* In his

[10] Ho, Peggy, P. et al., *Identification of Naturally Occurring Fatty Acids of the Myelin Sheath that Resolve Neuroinflammation,* 4 Sci. Transl. Med. 137ra73 (2012). [Pet. Ex. 10, Tab 8]. Dr. Steinman was one of the senior authors on this multifacility study. Tr.181

post-hearing report, Dr. Steinman recreated Figure 2D from the *Ho* article, which shows the lipids that were targeted by autoantibodies with green boxes around the polar head groups that were targeted on the left-hand side and red boxes around the polar head groups on lipids that were not targeted on the right. The arrows are pointing to the phosphate polar head groups.



Pet. Ex. 16 at 8; Pet. Ex. 10, Tab 8 at 4. The authors explained further, "Thus, binding of relapsing and remitting MS CSF autoantibodies to these lipids is dependent on the presence of (i) a nonbulky polar head group such as a phosphate group and (ii) at least one long hydrocarbon side chain." Pet. Ex. 10, Tab 8 at 3. *Ho* concluded:

> …the polar head groups are the lipid components targeted by the auto-antibodies, the fatty acid side chains are the components that mediate the lipids' anti-inflammatory effects. Furthermore, we find that the levels of these autoantibody-targeted lipids are lower in lesions from MS brain than in tissue from healthy brain. Autoantibody targeting may thus reduce the lipids' anti-inflammatory effect by enhancing their clearance or inhibiting their activity-and thereby compromise the lipid-mediated protection against neuroinflammation….

Pet. Ex. 10, Tab 8 at 9. Dr. Steinman testified that the study found that the fatty acid side chains can be protective, but when the immune system attacks the myelin in MS patients, it does not attack the fatty acids, but rather the phosphate group on glycerol. Tr. 34. Importantly, the authors observed that, "The destruction of myelin involves anti-lipid autoantibodies, which can induce demyelination and prevent remyelination in the mouse models of MS." *Id.*; Pet. Ex. 16 at 5; Tr. 182.

Dr. Steinman explained the relevance of the *Ho* article in the context of his theory, "this component of a phospholipid, phosphoglycerol, it's real in myelin that's attacked, but it's also real in Prevnar 13. And as the patent calls it….it's the nonsaccharide component. And that non-saccharide component is phosphoglycerol. Without it 18C is not immunogenic." Tr. 171.

Dr. Steinman also referenced an older article by *Gilburd* which sought to investigate autoantibodies in GBS by testing the reactivity of GBS sera with various phospholipids which are known constituents of myelin and serve as autoantigens in other autoimmune conditions. Pet. Ex. 10, Tab 14 at 1. They found that six out of sixteen GBS sera studied had antibodies to one or more of the phospholipid antigens. *Id.* The authors speculated, "…the reactivity of 6 out of the 16 GBS sera with the different antigens tested may be produced by a cross reaction of autoantibodies to [a] yet unidentified myelin constituent." *Id.* at 5-6. The authors noted that they did not find a significant association between the presence of specific antiphospholipid antibodies or anti-DNA antibodies in GBS when compared to controls. The authors theorized that the autoantibody production was more likely resulting from the myelin damage and the liberation of various myelin antigens into circulation. *Id.* at 6. Dr. Steinman testified that *Gilburd* shows that patients with GBS have autoantibodies to the phosphoglycerol. Tr. 37.[11] In his post-hearing report, Dr. Steinman explained that the authors of *Gilburd* did not provide an explanation as to why they thought that the autoantibodies did not cause an attack on the myelin, and that he only used the information in *Gilburd* in his theory to "emphasize that antibodies to these structures have been measured in humans with GBS." Pet. Ex. 16 at 12. He stated that the actual data in *Gilburd* shows evidence that phospholipids in myelin are targeted by antibodies in GBS. *Id.* at 13.

Dr. Steinman explained that *Ho*, published seventeen years after *Gilburd*, builds upon the data from *Gilburd*. He wrote, "The advantage of hindsight and further research by the team of 21 scientists in *Ho*, allowed us[12] to re-interpret the data in *Gilburd*, and to provide a rationale for simply not accepting the *Gilburd* authors speculation that such antibodies were the result, not the cause of GBS." Pet. Ex. 16 at 13. He stated that, "In *Ho* we showed that antibodies to six different myelin phospholipids, all target the phosphoglycerol head group, a constituent common to different myelin phospholipids with different fatty acid side chains. Antibodies to the phosphoglycerol head group can also explain the data in the *Gilburd* paper, as the analysis showed in the paper by *Ho*." *Id.* In his post-hearing report, Dr. Steinman summarized his theory as the following:

> The crux of my testimony in the courtroom was that petitioner's theory exemplifies how molecular mimicry to a component of the Prevnar[13] vaccine, known as phosphoglycerol, is implicated, in how an immune response to the vaccine could culminate in GBS. The immune response to phosphoglycerol in the vaccine targets the phospholipids in the myelin sheath of the nervous system. The theory describes how an immune attack on a critical component of the Prevnar 13 vaccine known as

[11] The *Gilburd* article referenced phosphatidylcholine, phosphatidyl-enthanalomine and phosphatidyl-serine. Dr. Steinman explained that a phosphoglycerol also contains a choline, which it can be either a phosphogylcerol or phosphocholine, but "the core is phosphoglycerol." Tr. 167.
[12] Dr. Steinman was one of the senior authors in the *Ho* study.

phosphoglycerol, which is itself a key substituent of a phospholipid, can induce an attack on the phospholipids in myelin.

Pet. Ex. 16 at 1.

Dr. Steinman stated that his theory of cross reactivity by molecular mimicry was based upon the review of the Prevnar-13 patent, which "unmistakably points to the importance of the phosphoglycerol in the composition," and three peer reviewed articles which explain how an immune response to phosphoglycerol can target phospholipids in the myelin membrane and lead to demyelination. Pet. Ex. 16 at 17.

2. Dr. Leist's opinion on medical theory of causation

Dr. Leist agreed that petitioner had the Miller-Fisher variant of GBS. Resp. Ex A. However, he opined that "there is no relationship between" the Prevnar 13 vaccine and petitioner's diagnosis. Resp. Ex. A at 6. He stated that, "Dr. Steinman asserts that vaccinations induce anti-myelin antibodies but provides no evidence that (a) Prevnar causes such antibodies and (b) that they are of pathophysiologic significance. *Id.* at 6. In his post-hearing report, Dr. Leist contended, "….phospholipids are not a listed constituent of the Prevnar-13 vaccine; that the Prevnar-13 vaccine is not a recognized cause of Guillain-Barre syndrome; and that [Dr. Steinman's] theory is speculative, without any reliable medical support." Resp. Ex. E at 3. Dr. Leist's opinion was that "no reliable theory has been presented to causally link Prevnar with Guillain-Barre syndrome at this point." Tr. 151.

Dr. Leist wrote that, "As an initial matter, (1) the purification processes of bacterial-strain-specific polysaccharides and carrier protein; and (2) the description of the chemical reaction by which the purified polysaccharides are covalently bound to the carrier protein, make it clear that phospholipids are not expected to be a component of the Prevnar-13 vaccine." Resp. Ex. E at 3. Dr. Leist testified that during the hearing, petitioner's theory shifted away from phospholipids to the sugar moieties that are in all the saccharides that are part of the vaccine. Tr. 71. He testified that Dr. Steinman's new theory was solely focused on the phosphoglycerol residue…here on one of the sugars….as the potential inciting agent." Tr. 79. Dr. Leist criticized Dr. Steinman's theory, stating:

> Since phosphoglycerols are sidechains in certain polysaccharides, Dr. Steinman holds that his theory of a putative autoreactive immune response against phospholipids would therefore also extend to such polysaccharides. Lost in this illogical chain of arguments is the fact that phospholipids are not a listed constituent of Prevnar-13 vaccine; that Prevnar-13 vaccine is not a recognized cause of Guillain-Barre syndrome; and that his theory is speculative, without any reliable medical support. At base, Dr. Steinman appears to take disparate aspects of our current medical understanding of the Prevnar-13 vaccine, and demyelinating conditions more broadly, to make inferential, conclusory leaps to opine that the Prevnar-13 vaccine can cause Guillain-Barre syndrome.

Resp. Ex. E at 3.

Dr. Leist was able to clearly explain the chemical structure of a phospholipid, describing in detail during the hearing and in his post-hearing report the relationship between a phosphoglycerol and a phospholipid. Tr. 102-106; Resp. Ex. E at 2-3. In his supplemental report, Dr. Leist explained that phospholipids and glycolipids are major components of all cell membranes. Resp. Ex. D at 3. He stated that, "The phospholipid molecule generally consists of two hydrophobic fatty acid 'tails' and a hydrophilic 'head' consisting of a phosphate group." *Id.* at 3. In his post-hearing report, Dr. Leist wrote, "Phosphoglycerol is a molecular component, or a building block of phospholipids, and is *not* a class of phospholipids. Phosphoglycerol does not contain lipids/fatty acids." Resp. Ex. E at 1. Dr. Leist explained that, "Phospholipid molecules are constructed from four components: fatty acids; a platform such as glycerol to which the fatty acids are attached; a phosphate; and an alcohol attached to the phosphate." *Id.*; Tr. 106. He further explained, "A phosphoglycerol is composed of a glycerol and a phosphate unit and is a building block (or component) of a phospholipid, but it does not contain lipids/fatty acids. *Id.* at 1-2. He testified that "the phosphoglycerol is not synonymous with a phospholipid or for that matter phosphoglycerides." Tr. 75.

It is not entirely clear why Dr. Leist continued to argue that *phospholipids* were not a component of the vaccine in his post hearing report, as Dr. Steinman's theory focused on mimicry between the *phosphoglycerol component* in the vaccine and that same molecule attached to the phospholipids in myelin. He did not contend that there are phospholipids in the vaccine.

Dr. Leist, referring to the *Chang* article and the diagram of the chemical composition of part of the Prevnar vaccine, explained that it depicts a "particular series of sugars," repeated several times and that Dr. Steinman circled, "the phosphoglycerol residue that is attached to a sugar, as a modification of this particular sugar, of the saccharide." Tr. 78. He noted that at the bottom of the graph is the O-acetyl, which he explained was, "…another modification residue or additional residue of the sugar moiety that also has been recognized by the authors of *Chang* as important in order for the vaccine to have biological effect against the specific strain of the bacteria." Tr. 78.

Dr. Leist testified that *Chang* looked at the relevance of the O-acetyl and the phosphoglycerol group regarding the antigenicity of the capsular polysaccharide, the 18C capsular polysaccharide. Tr. 82. He testified, "…there is literature indicating that if one [sugar moiety] loses this phosphoglycerol group, the resulting vaccine or the resulting immune response is no longer protecting against that particular strain of bacteria." Tr. 80. Dr. Leist attempted to distinguish between his opinion and Dr. Steinman's opinion regarding the importance of the phosphoglycerol attachment by stating, "…it is not that we don't know whether there's an immune response against the sugar. We just know that the immune response against the sugars that lost the phosphoglycerol is no longer protecting against this particular bacterial strain." Tr. 80. Confusingly, Dr. Leist appears to concede that the loss of the phosphoglycerol side chain would cause a loss of protective immunity while speculating that there may still be an ineffective immune response or perhaps that only immunogenicity to 18C would be lost. In his post-hearing report, Dr. Leist clarified his testimony, stating,

> "…Dr. Steinman specifically names the fact that the surface polysaccharide of the 18C pneumococcus pneumoniae isolate contains phosphoglycerol side chains that need to be preserved in order to induce a protective antibacterial immune response. As I testified, the phosphoglycerol side chains are required to induce protective immunity against streptococcus pneumoniae-18C.

Resp. Ex. E at 4. Dr. Leist interpreted *Chang* to mean, "Through the process of purification, this 18C-derived saccharide may now change. And they looked at what changes would be introduced during the purification process that would interfere with the saccharide that is now integrated into the vaccine to actually serve to generate protective immunity. And they identified in their work that this phosphoglycerol group and also the acetyl group are important to convey protective immunity. And if I correctly interpret their work, it is that they obviously purport that this is something that would need to be checked for during the manufacturing process that these groups are not lost…..especially the phosphoglycerin." Tr. 81. Dr. Leist stated, "Based on the observation of *Chang* for the vaccine to be protective against pneumococcus pneumoniae strain 18C, the phosphoglycerol polysaccharide side chain needs to be present." Resp. Ex. E at 5; Tr. 88.

Despite this concession, he testified that *Chang* did not address whether there is still an immune response if the phosphoglycerol component was lost, but instead "they just showed that it was not a protective immune response." Tr. 82. He testified that if "you take away this group (phosphoglycerol component) doesn't mean that now this becomes injurious or even antibodies would be induced, that those antibodies would be injurious throughout the process." Tr. 88. In his post-hearing report, he argued that, "*Chang does not*, provide a link between the purified surface polysaccharide, an apparent immune response against phospholipids (which are not present in the Prevnar-13 vaccine), and Guillain-Barré syndrome." Resp. Ex. E at 4.

He stated, "What is known is that the Prevnar-13 vaccine, which contains saccharides with phosphoglycerol side chains, and wild-type pneumococcus pneumonia strains, some of which contain saccharides with phosphoglycerol side chains, are not recognized as causes of Guillain-Barré syndrome." *Id.* at 5. He testified that, "…at this point in time, I don't think we allege that Mr. Koller *suffered* a pneumococcal infection with 18C." Tr. 88.

Dr. Leist also argued that the *Gilburd* article does not support petitioner's theory that antibodies against phospholipids caused demyelination in patients with GBS. Resp. Ex. E at 5. Dr. Leist asserted that because there are no listed phospholipids in the Prevnar-13 vaccine, antibodies generated by an immune response to the vaccine, could not then be targeting the phospholipids identified in *Gilburd* and moreover, *Gilburd* concludes that the autoantibodies to phospholipids in GBS patients was a result of myelin damage, not a product of inflammatory demyelination. Resp. Ex. E at 5.

Similarly, Dr. Leist argued that *Ho* does not support Dr. Steinman's theory because the authors, including Dr. Steinman, did not show that antibody reactivity against a phosphate group attached to a phospholipid caused disease. Resp. Ex. E at 5. Dr. Leist repeated that phospholipids are not in the Prevnar-13 vaccine. *Id.*

Dr. Leist stated, "Dr. Steinman provides no information on whether pneumococcus pneumonia is a recognized cause of Guillain-Barre syndrome….The FDA has not required inclusion of Guillain-Barré as a risk associated with the Prevnar-13 vaccine in the prescribing information; and Dr. Steinman does not discuss whether in his opinion the FDA erred in not requiring this." Resp. Ex. E at 6. Dr. Leist argued that the Prevnar-13 vaccine "has not been associated with Guillain-Barre syndrome, and that the few case reports in the literature do not provide information beyond temporality." *Id.* at 7.

During the hearing, Dr. Leist discussed an article by *Haber et al*., which reviewed adverse events reports following Prevnar-13 vaccination in adults 19 years and older in the Vaccine Adverse Event Reporting System ("VAERS") from June 2012 to December 2015. Tr. 125-29; Resp. Ex. C, Tab 1.[13] Dr. Leist testified that the article demonstrates that 60 million doses of the vaccine were administered and that eleven cases of GBS were reported to VAERS. Tr. 128-29. Dr. Leist testified that, "…there was not a causation of these cases." Tr. 129. The article states that they found eleven cases of possible GBS after PCV13 in which the median onset interval of symptoms was 9 days, the median age of patients was 68 years old, and ten cases were male. Resp. Ex. C, Tab 1 at 4. Additionally, the authors found that out of the eleven reported GBS cases, only one patient received an additional vaccine. *Id.* The authors stated, "Our study verified 11 GBS reports with symptom onset within 42 days of PCV13 vaccination with a reporting rate of 0.7 cases per million doses of vaccine distributed among adults aged 19 years and older." *Id.* at 5. They concluded that there was no disproportionate reporting of GBS following the PCV13 vaccine. *Id.* Dr. Leist testified that the *Haber* article demonstrated that there were eleven cases of GBS reported to VAERS post-Prevnar 13 vaccination, but that, "there was not proof of causation of these cases." Tr. 129.

Dr. Leist acknowledged that there are reporting biases in the VAERS data.[14] Tr. 125. He explained that VAERS is a passive reporting system and stated that, "….nobody can claim that there is a hundred percent reporting or what the exact number is." *Id.* Dr. Leist also recognized that in the present case, petitioner's physicians submitted a VAERS report. Tr. 127. Further, the authors of the *Haber* article also noted that reviewing VAERS data has limitations including, "underreporting, varying quality of reports…and the lack of an unvaccinated comparison group." Resp. Ex. C, Tab 1 at 5. The authors explained, "Because of these limitations, it is extremely difficult to determine causal associations between vaccines and adverse events." *Id.*

[13] Haber, P, et al., *Post-licensure surveillance of 13-valent pneumococcal conjugate vaccine (PCV13) in adults aged ≥ 19 years old in the United States, Vaccine Adverse Event Reporting System ("VAERS"), June 1, 2012-December 31, 2015,* 34 Vaccine 6630-6334 (2016). [Resp. Ex. C, Tab 1].

[14] I observed that the VAERS reporting system is a passive reporting system in which significant underreporting and mixed quality of reports provides little insight to causation. Tr. 124. This is consistent with other cases in the Vaccine Program, which have explained that VAERS has limited value due to the manner in which it is collected, the lack of confirmation of the reported information, and the lack of any systemic analysis. *See Capizzano v. Sec'y of Health & Human Servs.*, 63 Fed. Cl. at 231; *see also Tompkins v. Sec'y of Health & Human Servs.*, No 10-261V, 2013 WL 3498652, at *9 n.25 (Fed. Cl. Spec. Mstr. June 21, 2013), *mot. for review denied*, 117 Fed. Cl. 713 (2014) (The data provided by VAERS does not illustrate a causal connection; rather VAERS exists to identify signals to prompt further scientific investigation into potentially rare serious adverse events).

Dr. Leist agreed with Dr. Steinman's general description of molecular mimicry and he agreed with the general principle of molecular mimicry. Tr 95, 101. He noted that Dr. Steinman discussed GBS developing after certain strains of *c. jejuni* and appeared to accept Dr. Steinman's description. Tr. 95. He stated, "Much of the molecular mimicry that is normally discussed in situations such as this one is protein based, where the protein has a certain structural homology. Here we are purporting that the sugar moieties, in the bacteria on the pathogens may have such a sequential homogeneity, but there is no information that this actually occurs…within the constraints of this case." Tr. 96. In his post-hearing report, he criticized Dr. Steinman's theory, stating, "…that a phosphoglycerol present in whatever form in the vaccine could induce an immune response that cross-reacts with a phosphoglycerol unit contained in phospholipids, and thereby induce or cause Guillain-Barre syndrome," cannot "withstand even the most superficial examination, and it is without scientific foundation." Resp. Ex. E at 7.

Dr. Leist concluded his post-hearing report by stating, "Critically, Dr. Steinman does not propose that a single amino acid, or its side chain, would be sufficient for molecular mimicry. A claim that the presence of a particular (naturally occurring) amino acid in a protein by itself is sufficient to invoke molecular mimicry is scientifically unsustainable. But that is exactly what Dr. Steinman proposes in this case concerning phosphoglycerol, and its presence as a component in phospholipids and in select polysaccharides." Resp. Ex. E at 8.

3. Discussion and Conclusion of *Althen* prong one

Petitioner's theory, offered by Dr. Steinman, is that molecular mimicry is the likely causal mechanism of petitioner's GBS. He opined that an immune system cross-reactive response to a critical component of the Prevnar-13 vaccine, phosphoglycerol, which is itself a key substituent of phospholipids in myelin, can induce an attack on the phospholipids in myelin. Pet. Ex. 16 at 1. Respondent argued that Dr. Steinman's theory is unpersuasive because he shifted the focus of his theory from his original written reports during the entitlement hearing and his "inability to cogently articulate and expound upon his purported theory of the case." Resp. Post-Hearing Brief at 4. I agree that the earlier use of the term "phospholipid" caused initial confusion, but through questioning in the hearing, the experts came to a definitional agreement about the distinction between phospholipids and phosphoglycerol. After the definitional agreement and clarification from Dr. Steinman on petitioner's proposed theory of causation, I find that petitioner has provided preponderant evidence that the Prevnar-13 vaccine can cause Guillain-Barré syndrome based on molecular mimicry between the *phosphoglycerol* in the vaccine and the same in myelin as proposed by Dr. Steinman.

Dr. Steinman was able to identify that the Prevnar-13 vaccine not only includes a phosphoglycerol component, but that the phosphoglycerol is essential for the vaccine to be effective by referencing the patent for Prevnar-13 and the article by *Chang*. *Chang* explained that the18C serotype is a complex structure composed of "a repeating unit having a tetrasaccharide backbone with d-galactose highly branched by D-glucose and glycerol phosphate." Pet. Ex. 10 at 3; Pet. Ex. 16 at 15; Tr. 167. *Chang* also explained that the glycerol-phosphate side chain must be preserved in the manufacturing process to conserve an adequate immune response to 18C. Pet. Ex. 27; Resp. Ex. D at 1. Additionally, Dr. Steinman observed that the Prevnar-13 patent application explains the importance of retaining the phosphate or

glycerol phosphate side chains during conjugation and is included in more than just the serotype 18C, but also is documented in other serotypes present in the vaccine. Pet. Ex. 16 at 10; Pet. Ex. 12 at 34. The patent application provides, "An important consideration during conjugation is the development of conditions that permit the retention of potentially sensitive non-saccharide substituent functional groups of the individual components, such as 0-Acetyl, phosphate or glycerol phosphate." Pet. Ex. 12 at 34. Dr. Steinman later observed that it is not just serotype 18C that has glycerol phosphate side chains, but that serotypes 15B and 11A are also documented in the patent description to preserve it as well. Pet. Ex. 16 at 10-11. Dr. Steinman opined that it is highly likely that the other strains in the vaccine also preserve the phosphate group. Tr. 37.

Further, both experts agreed that retaining the glycerol phosphate side chains is necessary to confer immunogenicity to at least serotype 18C. Tr. 37; Tr. 88; Resp. Ex. E at 4-5. Specifically, Dr. Leist conceded that the phosphoglycerol side chains identified in the *Chang* article are required to induce protective immunity against *S.pneumoniae* 18C. Resp. Ex. E at 4; Tr. 176. However, Dr. Leist argued that it was "unknown whether antibodies against polysaccharides of pneumococcus pneumoniae strain 18C would bind to phospholipids in myelin, and if so, whether this interaction would lead to demyelination of peripheral nerves." Resp. Ex. E at 5. Dr. Leist is correct that the *Chang* article does not discuss the cross reactivity of the vaccine to myelin, but Dr. Steinman referenced the article as a first step in this theory to demonstrate that the phosphoglycerol is a necessary component of the vaccine for the development of immunogenicity. As a vaccine is obviously designed to generate a protective immune response, and the vaccine does contain the phosphoglycerol side chain, there appears to be no meaningful difference between Dr. Steinman's and Dr. Leist's interpretation of the *Chang article.*

To demonstrate that antibodies generated by the immune system's reaction to the phosphoglycerol in the Prevnar-13 vaccine can cause an immune reaction which leads to demyelination as seen in GBS, Dr. Steinman referenced the *Ho* article, in which the authors found that MS patients have antibodies that bind to a phosphoglycerol headgroup which is attached to lipids that make up the myelin. Pet. Ex. 10, Tab 8. The authors of *Ho* found that autoantibodies in multiple sclerosis target the phosphoglycerol polar head groups in the phospholipids in myelin, which may reduce the lipids' anti-inflammatory effect and compromise the lipid-mediated protection against neuroinflammation. Pet. Ex. 10, Tab 8 at 9; Resp. Ex. D at 9. It is significant that this finding in the *Ho* study was in actual MS *patients* who suffered demyelination associated with that disease.

Dr. Leist criticized the reliance on *Ho*, stating, "The authors showed antibody reactivity against the phosphate group in the context of the lipid structure. They did not show, however, that the phosphate group would be recognized on its own, or outside the lipid structure. The *Ho* authors also did not show that these antibodies caused disease." Resp. Ex. E at 3-4. The extent to which Dr. Leist would require specific proof is not required in this program to demonstrate a *theory* of causation in the Vaccine Program. However, contrary to his criticism, the authors in *Ho* actually demonstrated that lipids that lacked a phosphate group or contained a phosphate group connected to a bulky group (like a ring structure or a phosphate group linked to four carbons*) were not* targeted by autoantibodies in relapsing and remitting MS. Pet. Ex. 10, Tab 8

at 3. Further, the authors noted that the autoimmune response was directed to the phosphoglycerol side chains and may have contributed to demyelination by attenuating the protective effect of the attached fatty acid chains in the myelin. Pet. Ex. 10, Tab 8 at 9.

As noted above, Dr. Steinman also referenced *Gilburd*, which found antiphospholipid antibodies in six patients with GBS. Pet. Ex. Tab 14. Dr. Steinman stated that he referenced *Gilburd* because it showed the presence of antibodies to phosphotidylcholine and phosphotidylalanine, the core of which is the phosphoglycerol. Tr. 38, 167-68; Pet. Ex. 16 at 13. He acknowledged the authors in *Gilburd* came to a different conclusion, but also noted that the discoveries published in *Ho* seventeen years later, gave him the ability to analyze the Gilburd data differently. Pet. Ex. 16 at 3. He stated, "Antibodies to the phosphoglycerol headgroup can also explain the data in the *Gilburd* paper, based on the analysis showed by *Ho*. The commonality of all the different phospholipids is the glycerophosphate head, and antibody studies indicate that this is where the antibodies bind." *Id.* He opined that, "the antibody is actually directed to that component, the phosphate headgroup whether it's MS or GBS." Tr. 167.

Petitioner also submitted two articles which referenced case reports of patients developing GBS following streptococcus pneumonia infection and vaccination with the pneumococcal vaccines. *Khatib et al*., documented a case of GBS in a 13-year-old male who was positive for streptococcus pneumonia. Pet. Ex. 13.[15] The authors of the article observed, "GBS is an important cause of acute flaccid paralysis, due to a triggering factor infectious (like mainly campylobacter, cytomegalovirus, Epstein-Barr virus, Mycoplasma pneumoniae, influenzas-like illnesses), and non-infectious (like immunization, trauma, surgery and bone marrow transplants). This triggering factor evokes immune responses that cross-react with peripheral nerve components because of the sharing of cross-reactive epitopes (molecular mimicry), this immune response is directed toward the myelin or axon of the peripheral nerve." *Id.* at 3. The authors opined, "It is possible therefore that pneumococcus has antigens which triggered an immune response and cross-reacted with peripheral nervous system surface components due to molecular mimicry. This is due to natural transformation of Streptococcus pneumoniae's capsular polysaccharide." *Id.* Thus, the authors of the *Khatib* article endorsed the theory of molecular mimicry for a wild pneumococcus infection for inducing GBS.

The article by *Ravishanka*r described a case of a 66-year-old female who received a PCV13 vaccine in January 2015 and then a second dose of PPSV23 in August 2015 which contains many of the same antigens as the PCV13, and by September 2015 developed weakness and leg paralysis. Pet. Ex. 14.[16] She had evidence of mixed axonal and demyelinating sensorimotor polyradiculopathy, a GBS variant. *Id.* at 1. The author set forth a theory of autoimmunity; "The major mechanism resulting in the autoimmunity by adjuvanted vaccination has been proposed to be due to the epitopes of a vaccine that initiate the development of antibodies and/or T cells that could cross-react with the epitopes on myelin or axonal glycoproteins." *Id.* at 1-2. Further, the article explained Streptococcus pneumonia are,

[15] Khatib, H. et al., *Case Report: Guillain-Barre syndrome with pneumococcus-A new association in pediatrics,* 11 IDCases 36-38 (2018). [Pet. Ex. 13].

[16] Ravishankar, N, *Guillain-Barre Syndrome Following PCV Vaccine*, 4(1) J. Neurol Neurosurg. 134 (2017). [Pet. Ex. 14].

"polysaccharide-encapsulated, gram positive, lancet-shaped organisms and pneumococcal vaccines rely on these capsules to induce a serotype-specific immune response." *Id.* at 2. Further, the article described "The polysaccharide conjugated to a carrier protein uses an MHC class II dependent response to present the carrier protein to carrier-peptide-specific helper T cells. This leads to enhancement of the B-cell immune response, so that the antibody response is of greater specificity and functionality." *Id.* at 2. The article concluded, "Thus, it can be inferred that the conjugated vaccine produces the enhanced B-cell immune response leading to autoimmune reaction to the peripheral nerves." *Id.* While case reports cannot establish causation, they provide some evidence of causation. *Coleman v. Sec'y of Health & Hum. Servs.*, No. 18-352, 2021 WL 1291677 (Fed. Cl. Spec. Mstr. Feb. 16, 2021). The author of the article appears to endorse a theory of molecular mimicry between components of the pneumococcal vaccines with components of the myelin in the nervous system, consistent with Dr. Steinman's theory.

The theory of molecular mimicry offered by Dr. Steinman in this case is not novel and not unfamiliar in cases argued before this Court. Molecular mimicry has been accepted in the Vaccine Program as a sound and reliable medical theory and has been persuasively linked to different immune-mediated demyelinating conditions. *See e.g. Stitt v. Sec's of Health & Hum. Servs.*, No. 11-140V, 2013 WL 3356791, at *8-9 (Fed. Cl. Spec. Mstr. May 31, 2013) (finding petitioner's biological mechanism of molecular mimicry demonstrated that the flu vaccine could cause GBS); *Roberts v. Sec'y of Health & Hum. Servs.,* No. 09-427V, 2013 WL 5314698 (Fed. Cl. Spec. Mstr. Aug. 29, 2013) (finding that Tdap vaccine led petitioner to develop transverse myelitis via molecular mimicry); *Salmins v. Sec'y of Health & Hum. Servs.*, No. 11-140V, 2014 WL 1569478 (Fed. Cl. Spec. Mstr. Mar. 31, 2014 (finding that HPV vaccine caused petitioner to develop GBS via molecular mimicry); *Spayde v. Sec'y of Health & Hum. Servs.,* No. 16-1499V, 2021 WL 686682 (Fed. Cl. Spec. Mstr. Jan. 27, 2021) (finding that molecular mimicry is a sound and reliable theory for the influenza vaccine to cause GBS). *Reinhardt v. Sec'y of Health & Hum. Servs.*, No. 17-1257V, 2021 WL 1851491 (Fed. Cl. Spec. Mstr. Apr. 2, 2021) (finding that the flu vaccine caused petitioner's optic neuritis).

Dr. Steinman acknowledged that most of the other cases involving molecular mimicry involved protein homology and not often sugars. Tr. 50. In those cases, in which he testified, he demonstrated homology through Blast searches of protein peptides in the vaccines and in the nervous system. *See Smith v. Sec'y of Health & Hum. Servs.*, No. 08-864V, 2016 WL 2772194 (Fed. Cl. Spec. Mstr. Apr. 18, 2016) (the special master accepted Dr. Steinman's protein-based theory of molecular mimicry between the vaccine and MS) and *Robinson v. Sec'y of Health & Hum. Servs.*, No. 14-952V, 2021 WL 2371721, at *8-10 (Fed. Cl. Spec. Mstr. Apr. 12, 2021) (Dr. Steinman proposed a theory of protein-based molecular mimicry for inciting MS post-flu vaccination). He testified in this case, that on one hand it is more challenging to discuss molecular mimicry in the world of sugars and lipids, but on the other it is an instance where he could show the actual chemical structure involved in the theory. Tr. 51. Importantly, he testified that the most well studied example of molecular mimicry and GBS was to the infection with the bacteria *c. jejuni*. Tr. 17. He explained that the classic example of molecular mimicry in GBS is with *c. jejuni*, which is molecular mimicry to a sugar. Tr. 50-51. In this case, Dr. Steinman noted that this case involves molecular mimicry with a specific component of the vaccine, the phosphoglycerol, which is attached to the sugar [in the vaccine] and the same phosphate group

attached to the phospholipids in myelin which *Ho* showed to be the point of attack in the myelin of MS patients. *Id*

Dr. Leist agreed with Dr. Steinman that molecular mimicry between *c. jejuni* and GBS has been accepted in the medical literature. Tr. 95.[17] But Dr. Leist argued, "much of molecular mimicry that is normally discussed…is protein based, where the protein has a certain structural homology… Here we are purporting that the sugar moieties, the bacteria on the pathogens may have such a sequential homogeneity, but there is no information that this actually happens." Tr. 96. Dr. Leist acknowledge that the vaccine is designed to induce an immune response against the bacteria and that the sugar moieties [in the vaccine] are not a complete reflection of what is on the native bacteria so you could "stretch the term molecular mimicry" because the anti-vaccine response is designed to protect by providing an immune response. Tr. 97. However, he stressed that there is not a "body of literature that links Prevnar-13 to the generation of GBS by molecular mimicry." *Id.*

Dr. Leist's argument that there is "no reliable medical literature supporting," petitioner's theory is unpersuasive. Resp. Ex. E at 5. Petitioner should not be faulted for the lack of published literature on point with his case. *Swaiss*, at *27. A petitioner can satisfy *Althen* prong one without having to provide epidemiologic studies or provide specific biological mechanisms. *See Andreu v. Sec'y of Health & Hum. Servs.*, 569 F.3d 1367, 1378-79 (Fed. Cir. 2009); *Althen*, 418 F.3d at 1280. Therefore, "a paucity of medical literature supporting a particular theory of causation cannot serve as a bar to recovery." *Andreu*, 569 F.3d at 1379. Instead, a petitioner's theory of causation must be supported by a reputable medical or scientific explanation and the assessment of whether a proffered theory of causation is "reputable" can involve the assessment of relevant scientific data. *Andreu*, 569 F. 3d at 1380-81 (citing *Althen* at 1278); *see also Knudsen*, 35 F.3d at 548 (requiring a "sound and reliable or scientific explanation"). In this case, petitioner presented medical literature that supported Dr. Steinman's theory of molecular mimicry. The defense based upon lack of epidemiological studies or lack of definitive proof of the medical theory linking the Prevnar-13 vaccine is unpersuasive and requiring proof of such, would impermissibly raise petitioner's burden.

The Federal Circuit recently explained that petitioners need to demonstrate a sound and reliable theory of causation, but it does not "require identification and proof of specific biological mechanisms." *Kottenstette*, ---Fed. Appx.---, 2021 WL 2434329 (Fed. Cir. June 15, 2021). Further, the Court reiterated that "proof of causation does not "require identification and proof of specific biological mechanisms[.]." *Id.*, at *7 (citing *Knudsen*, 35 F.3d at 549). Additionally, molecular mimicry has been accepted as a sound and reliable theory without

[17] This is consistent with other cases where special masters have recognized that *c.jejuni* infection can cause GBS through molecular mimicry. *See Isaac v. Sec'y of Health & Human Servs.,* No. 08-601V, 2012 WL 3609993, at *4 (Fed. Cl. Spec. Mstr. July, 30, 2012) (Observing that molecular mimicry has been used to explain the induction of GBS by a bacterium, *c.jejuni*); *Salmins v. Sec'y of Health & Hum. Servs.,* No. 11-140V, 2014 WL 1569478, at *13 (Fed. Cl. Spec. Mstr. Mar. 31, 2014) (noting that molecular mimicry is a generally accepted theory and Dr. Leist agreed molecular mimicry is a well-documented explanation for how *c.jejuni* can cause GBS); *Deshler v. Sec'y of Health & Hum. Servs.,* No. 16-1070, 2020 WL 4593162, at *20 (observing, "The parties appear to agree that molecular mimicry can also occur after exposure to certain bacterial antigens….Indeed much of the literature offered in this matter establishes that exposure to bacteria such as *c.jejuni* is associated with an increased risk of developing GBS via molecular mimicry.").

demonstrating specific homology between a vaccine and the autoimmune injury. *See Salmins*, at *14 (accepting molecular mimicry as an acceptable theory to satisfy *Althen* prong one without demonstrating specific homology between the vaccine and GBS); *Swaiss v. Sec'y of Health & Hum. Servs.*, No. 15-286V-2019 WL 6520791, at *26-27 (accepting molecular mimicry as a sound and reliable theory without requiring petitioner to demonstrate specific homology between the vaccine and small-fiber neuropathy). Requiring definitive proof or epidemiology would impermissibly raise the petitioner's burden of proof.

While not required to show a specific mechanism, Dr. Steinman identified homology between a non-sugar component of the pneumococcal vaccine and components in the myelin, as the focus of cross-reactivity, leading to demyelination. The three articles he cited to, *Chang, Ho,* and *Gilburd*, and the Prevnar-13 patent application, also demonstrate support for his theory. In particular, the *Ho* article identified that the phosphate group in phospholipids in myelin was targeted by auto-antibodies in MS patients apparently triggering demyelination. Dr. Steinman persuasively argued that the same cross-reactive mechanism triggered by the Prevnar-13 vaccine can cause similar demyelination in the peripheral nerves causing GBS.

The only other reasoned decision involving the Prenvar-13 vaccine and GBS is *Deshler*. In that case, the Chief Special Master concluded that he could not find causation between the vaccine and GBS based on the evidence presented in the case. *Deshler v. Sec'y of Health & Hum. Servs.*, No.16-1070, 2020 WL 4593162, at *21 (Fed. Cl. Spec. Mstr. July, 1, 2020). I have concluded that the evidence presented in this case is much more persuasive than what was presented by the petitioner in *Deshler*.

"[T]o require identification and proof of specific biological mechanisms would be inconsistent with the purpose and nature of the vaccine compensation program." *Knudsen*, 35 F.3d at 549. The 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 (emphasis added). As such, after reviewing the evidence submitted in this case, including the medical literature, expert reports and testimony during the hearing, I find that petitioner has presented a reputable scientific theory based on a sound and reliable scientific explanation, demonstrating that the Prevnar-13 vaccine can cause GBS, thus satisfying *Althen* prong one.

B. *Althen* prong two

Under *Althen* prong two, petitioner must prove "a logical sequence of cause and effect showing that the vaccination was the reason for [her] injury." *Althen*, 418 F.3d at 1278. This prong is sometimes referred to as the "did it cause" test; i.e. in this particular case, did the vaccine(s) cause the alleged injury. *Broekelschen*, 618 F. 3d at 1345 ("Because causation is relative to the injury, a petitioner must provide a reputable medical or scientific explanation that pertains specifically to the petitioner's case"). Temporal association alone is not evidence of causation. *See Grant v. Sec'y of Health & Hum. Servs.*, 9556 F.2d 1144, 1148 (Fed. Cir. 1992). This sequence of cause and effect is usually supported by facts derived from petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326; *Grant*, 956 F.2d at 1148. Treating physicians are likely to be in the best position to determine

whether a logical sequence of cause and effect show[s] that the vaccination was the reason for the injury. *Paluck v. Sec'y of Health & Hum. Servs.*, 786 F.3d 1373, 1385 (Fed. Cir. 2015) (quoting *Andreu*, 569 F.3d 1375).

Prior to receiving the Prevnar-13 vaccine, petitioner was a relatively healthy and active 65-year-old man. Petitioner received the pneumococcal conjugate vaccine on May 13, 2015 and then on May 27, 2015, approximately 14 days later, presented to the emergency department with left-sided facial weakness, a symptom of the Miller Fisher variant of GBS. Pet. Ex. 6 at 1. His symptoms became more widespread over the succeeding several days and included bilateral facial, weakness, diplopia and general weakness. On examination the doctors noted areflexia and significantly elevated protein in the cerebral spinal fluid all consistent with a diagnosis of the Miller Fisher variant of GBS.

Dr. Steinman opined that the Prevnar-13 vaccine has constituents that induce antibodies known to cross-react with the myelin and that are found in patients with GBS. Pet. Ex. 10 at 14. Dr. Steinman explained that molecular mimicry fits the present case because the phosphoglycerol component of the Prevnar-13 vaccine contains sufficient homology with the phosphate group in the myelin and that the phosphate group has been shown to be attacked in a similar autoimmune, neuroinflammatory, demyelinating disease. There were no alternative explanations such as concomitant infection to explain the stimulation of the immune response, and the timing of 14 days to onset is appropriate. Pet. Ex. 10 at 13; Pet. Ex. 16 at 1; Tr. 42.

Dr. Steinman observed that prior to the administration of the Prevnar-13 vaccine on May 13, 2015, petitioner had some health issues, in particular atrial fibrillation but never demonstrated any significant neurological deficits. Tr. 12. He testified that petitioner presented a "classic constellation" of symptoms, including neurological exam, laboratory tests that showed significantly elevated protein in the cerebral spinal fluid with few cells, involvement of the facial nerves and ultimately some involvement of petitioner's eye movements. Tr. 13-14. Dr. Steinman also observed that alternative causes were ruled out, including stroke, infection and vitamin B12 deficiency. Pet. Ex. 10 at 9; Pet. Ex. 6 at 26. Additionally, there were "no gastrointestinal symptoms…no diarrhea, and no fever identified." Tr. 15

Further, multiple treating physicians associated the onset of petitioner's Miller Fisher variant of GBS to the pneumococcal vaccination. *See* Pet. Ex. 6 at 69-70, 107; Pet. Ex. 3 at 6; Pet. Ex. 2 at 13. When petitioner was admitted to Theda Clark Medical Center on June 1, 2015, attending neurologist, Dr. Huder observed that petitioner had received the pneumococcal 13 vaccination a week and half prior to admission and noted petitioner had developed leg weakness two days prior to hospital admission. On the same day, when plasmapheresis was initiated, petitioner's diagnosis was, "Guillain-Barré syndrome following vaccination." Pet. Ex. 6 at 38. Petitioner's diagnosis of "Miller-Fisher variant Guillain-Barré syndrome after vaccination," did not change while he was hospitalized. *See* Pet. Ex. 6 at 31, 69-70, 94, and 107. The petitioner's discharge summary again noted that he had received a recent vaccination, stating, "The patient had a recent pneumococcal vaccine a week and half prior to admission." Pet. Ex. 6 at 103.

On July 3, 2015, petitioner had an appointment with his primary care physician, Dr. Bogner, for a follow-up following hospitalization. Pet. Ex. 3 at 6. Petitioner's diagnosis was

recorded as, "Guillain-Barré syndrome following vaccination." *Id.* Dr. Bogner also had noted that one of petitioner's active diagnoses was, "Miller-Fisher variant Guillain-Barré syndrome, following vaccination." *Id.* at 9.

On August 3, 2015, petitioner had a follow-up appointment with neurologist, Dr. Gizell Larson. Pet. Ex. 2 at 13. Dr. Larson wrote, "[Petitioner] was hospitalized for a very long time at Theda Clark with Miller Fisher variant of Guillain-Barré syndrome that developed within 1 week of receiving a pneumococcal vaccine." *Id.* Dr. Larson specifically related the cause of petitioner's GBS with the pneumococcal 13 vaccine, writing, "*I do believe that this is, indeed, due to pneumococcal vaccine*." *Id.* (emphasis added).

The onset of petitioner's symptoms and the progression of those symptoms is consistent with petitioner's theory that the phosphoglycerol component of the antigens in the Prevnar-13 vaccine caused an immune reaction involving a cross-reaction with the phosphoglycerol components of the myelin, leading to demyelination. Further, there was no evidence in the record to suggest that the onset of petitioner's Miller-Fisher GBS was the result of any other underlying condition and multiple treating physicians associated the Prevnar-13 vaccine as causing petitioner's injury. As explained below the timing was also consistent with the theory proposed. As such, petitioner has demonstrated by preponderant evidence a logical cause and effect, satisfying *Althen* prong two.

C. *Althen* prong three

Althen prong three requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen* at 1281. That term has equated to the phrase, "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Hum. Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one). *Id.* at 1352.

Petitioner argues that the onset of his GBS symptoms, which began between nine and fourteen days after receiving the Prevnar-13 vaccination demonstrate a proximate temporal relationship between the vaccine and the onset of petitioner's GBS. Pet. Post-Hearing Brief at 17-18. Dr. Steinman stated that the medically acceptable timeframe between vaccination and onset of GBS was between a few days to about six or seven weeks. Tr. 41.; Pet. Ex. 8 at 8-9. He stated that there is an increased incidence of GBS in the time frame between one to seven weeks is consistent with what is seen for onset of GBS following the influenza immunization. Pet. Ex. 8 at 9. He noted that the timeframe of a few days to six or seven weeks for GBS following the 1976 swine flu immunization is often used as a surrogate in other cases, as it has been the most extensively studied relationship. Tr. 41.; Pet. Ex. 8 at 9. Dr. Steinman cited to an article by *Schonberger et al.,* which found that following the receipt of the 1976/1977 flu vaccine there

was an increased risk of GBS within the 5-week period post-vaccination, although the increase risk lasted for approximately 9 to 10 weeks. Pet. Ex. 10, Tab 17 at 1.[18]

Respondent argued that the relationship of the onset of petitioner's symptoms and the Prevnar 13 vaccine was "more likely coincidental." Resp. Post-Hearing Brief at 17. Dr. Leist stated that, "The time interval observed with forms of influenza in 1976/1977 is not applicable to forms of conjugated pneumococcal vaccine." Resp. Ex. A at 5. He stated that Prevnar-13 and the 1976/77 forms of influenza vaccine have different compositions. *Id.* During his testimony, he contended that the influenza is a split viral vaccine and the Prevnar 13 vaccine "is made of well-controlled ingredients that are highly purified. So, any comparison between the influenza vaccine and the Prevnar [13 vaccine] [can] only go so far." Tr. 111-12. While Dr. Leist stated the obvious that Prevnar and influenza are different vaccines, there does not appear to be any reason that the timing of an autoimmune cross reaction would necessarily be different. As observed above, most of the petitioner's treating physicians considered the time frame to be appropriate.

Dr. Leist also acknowledged that the *Haber* article, discussed above, found 11 cases following Prevnar-13 vaccination, with the median onset interval of symptoms to be nine days (the range from 2-34 days). Resp. Ex. C, Tab 1 at 4. Further, Dr. Dr. Leist testified that the 42-day time interval that was found to be biologically plausible between the 1976/1977 influenza vaccine and GBS was applied by the authors in the *Haber* study because, "it's the best information we have." Tr. 128-29. Later, he explained that he did not know if the "influenza experience is actually applicable to a polysaccharide vaccine." Tr. 142. But he conceded that information specific to the Prevnar-13 vaccine is not available, stating "Everything that we know about timing between vaccines and Guillain-Barré Syndrome comes from the observation with the influenza vaccine." *Id.*

Both Dr. Steinman and Dr. Leist acknowledged that there is a lack of studies, outside of the *Schonberger* study, which would provide a timeframe for the onset of GBS following vaccination. Tr. 41; Tr. 142. Dr. Leist, conceded that the generally accepted timeframe of a 42-day time interval found to be biologically plausible with the influenza vaccine was a reasonable timeframe to use. Tr. 128-29. Specifically, Dr. Leist testified that the use of the 42-day timeframe the authors used in the *Haber* article to examine reports of injuries post pneumococcal vaccination was a "reasonable standard," and that the authors use of the 42-day timeframe was based on the 1976/1977 influenza program, "because it's the best information we have." Tr. 128-29.

In this case, the onset of petitioner's symptoms occurred approximately 12-14 days following the receipt of his Prevnar-13 vaccination on May 13, 2015. On May 27, 2015, fourteen days post-vaccination, petitioner reported to the Theda Clark Emergency Department with complaints of headache, body aches and difficulty sleeping which began two days ago. Pet. Ex. 6 at 1. Petitioner also reported that he developed left-sided facial droop while brushing his teeth in the morning of May 27, 2015. *Id.* Thus, petitioner's symptoms, which presented at a minimum of 12 days post-vaccination is consistent with the *Haber* article's finding that onset of

[18] Schonberger, L., et al., *Guillain-Barre Syndrome Following Vaccination in the National Influenza Immunization Program, United States, 1976-1977,* 110 Am. J. of Epidemiology 105-123 (1979). [Pet. Ex. 10, Tab 17].

GBS post-Prevnar 13 vaccination occurred between 2-34 days and is fairly close to the median time frame of onset noted in that study. Additionally, the onset of petitioner's symptoms occurred within the medically accepted timeframe consistent with petitioner's theory of molecular mimicry that has been accepted in other Vaccine Program cases. *See Reinhardt v. Sec'y of Health & Hum. Servs.*, 2021 WL 1851491, at *18 (finding the onset of injury twelve days post vaccination is an acceptable timeframe in which to infer causation); *Spayde v. Sec'y of Health & Hum. Servs.*, 2021 WL 686682*19 (finding an onset of GBS symptoms eight weeks post-vaccination is appropriate given the causal mechanism of molecular mimicry.); *Robinson v. Sec'y of Health & Hum. Sers.*, No. 14-952, 2021 WL 2371721, at *22 (Fed. Cl. Spec. Mstr. Apr. 12, 2021) (finding that an onset of symptoms for multiple sclerosis of 13 days post-vaccination is a medically acceptable timeframe to infer causation given the mechanism of molecular mimicry).

Based on the existing medical literature, expert testimony, and medical records, petitioner has demonstrated that the onset of GBS 12 to 14 days after receiving the Prevnar 13 vaccine is an acceptable timeframe in which to infer causation. As such, petitioner has satisfied the third *Althen* prong.

V. Conclusion

Based on the record as a whole, including medical records, the petitioner's expert opinion, and the submitted medical literature, I find that petitioner has persuasively established a sound and reliable theory to establish by preponderant evidence proof of the three *Althen* prongs and to establish that petitioner's May 13, 2015 Prevnar-13 vaccination caused his Miller-Fisher GBS. Thus, I find petitioner has established by preponderant evidence that he is entitled to compensation. A separate damages order will be issued.

IT IS SO ORDERED.

s/Thomas L. Gowen
Thomas L. Gowen
Special Master