In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 18-386V

Filed: July 18, 2024

* *

WILLIAM MORRISON,

Petitioner,

v.

SECRETARY OF HEALTH AND HUMAN SERVICES,

Respondent.

* *

Anne Toale, Maglio Christopher and Toale, Sarasota, FL, for Petitioner
Adam Muffett, U.S. Department of Justice, Washington, DC, for Respondent

DECISION ON ENTITLEMENT[1]

Oler, Special Master:

On March 13, 2018, William Morrison ("Petitioner") filed a petition for compensation under the National Vaccine Injury Compensation Program, 42 U.S.C. § 300aa-10, *et seq.*[2] (the "Vaccine Act" or "Program"). The petition alleges that Mr. Morrison developed Miller-Fisher syndrome, a variant of Guillain-Barré syndrome ("GBS"), as a result of the pneumococcal ("Prevnar 13") vaccine he received on September 3, 2015. Pet. at 1-2. For the reasons discussed

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

[2] National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755. Hereinafter, for ease of citation, all "§" references to the Vaccine Act will be to the pertinent subparagraph of 42 U.S.C. § 300aa (2012).

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in this decision, I find that Petitioner has not demonstrated that the Prevnar vaccine can cause GBS. The petition is accordingly dismissed.

I. Procedural History

Petitioner filed his petition on March 13, 2018. Pet., ECF No. 1. He filed medical records on May 11, 2018, followed by a statement of completion. ECF Nos. 7-8.

Respondent filed his Rule 4(c) Report on April 2, 2019 indicating that the case was not appropriate for compensation under the Vaccine Act. Resp't's Rep. at 1; ECF No. 18.

Petitioner then filed additional medical records. ECF Nos. 24, 26, 32, 34, 35. Petitioner filed an expert report from Dr. Lawrence Steinman on October 9, 2020. Ex. 24; ECF No. 40. On March 29, 2021, Respondent filed responsive expert reports from Dr. J. Lindsay Whitton and Dr. Brian Callaghan. Exs. A, D; ECF Nos. 47, 48.

On July 9, 2021, Petitioner filed a supplemental report from Dr. Steinman. Ex. 59, ECF No. 51. On January 3, 2022, Respondent filed responsive reports from Drs. Whitton and Callaghan. Exs. G, H; ECF Nos. 55-56. Respondent filed an amended report by Dr. Whitton on January 18, 2022. Ex. F, ECF No. 59. On June 10, 2022, Petitioner filed a supplemental report from Dr. Steinman. Ex. 70, ECF No. 65.

The parties indicated that they wished to file briefs for a ruling on the record. ECF No. 64. The parties later indicated via email that they wished to proceed to an entitlement hearing. I scheduled the case for a hearing to take place on March 29-30, 2023. *See* non-PDF Scheduling Order dated June 10, 2022.

I conducted an entitlement hearing on March 29-30, 2023. Petitioner filed a post-hearing brief on May 10, 2023. ECF No. 104. Respondent filed a response on June 9, 2023. ECF No. 106. Petitioner filed a reply brief on June 27, 2023. ECF No. 111.

This matter is now ripe for adjudication.

II. Medical Records

I note that Petitioner's diagnosis, the Miller-Fisher variant of GBS, is not contested by the parties, therefore I will only summarize the medical records pertinent to the development of Petitioner's condition, severity, and course of treatment.

A. Relevant Pre-Vaccination History

Petitioner was 79 years old at the time of vaccination. His prior medical history includes Type II diabetes, hyperlipidemia, hypertension, gout, obesity, coronary artery disease, osteoarthritis, and hypothyroidism. Ex. 1 at 1-2; Ex. 7 at 173. Mr. Morrison previously underwent two cardiac catheterization procedures and was previously a heavy smoker and drinker, quitting both habits about 20 years ago. Ex. 7 at 173, 336. Petitioner had previously received the

pneumococcal polysaccharide vaccine (PPSV) in 2009. *Id.* at 26. His receipt of this vaccine was uneventful. On September 3, 2015, Petitioner was seen by Dr. Sujata Soni at the Philadelphia VA Medical Center for a "primary care follow up." Ex. 1 at 1-6. Petitioner received the allegedly causal pneumococcal conjugate ("Prevnar 13") vaccine during this visit. *Id.* at 1.

B. Post-Vaccination History

On September 13, 2015, Petitioner presented to the Kennedy Health System emergency department and was seen by Dr. Matthew Young, D.O., for abdominal pain. Ex. 7 at 172-73. Under History of Present Illness ("HPI"), Petitioner complained of diffuse lower abdominal pain lasting the past four days, nausea, and that he had not had a bowel movement in the last three days. *Id.* at 172. Petitioner denied fever, diarrhea, or vomiting. *Id.* at 172-74. Petitioner was discharged with an assessment of abdominal pain of unknown cause with instruction to follow up with his PCP. *Id.* at 183.

Petitioner returned to the emergency department later that same day for worsening lower abdominal pain, with abdominal distension, nausea, and vomiting. Ex. 7 at 227-38. Petitioner reported additional symptoms of nausea, vomiting, and a four day history of constipation. *Id.* at 228. A radiology report found a "nonspecific mild gaseous distention of the large and small bowel possibly ileus." *Id.* at 234. Petitioner was admitted for abdominal pain and an ileus and was treated with IV fluids, bowel rest, and analgesia. *Id.* at 241-42.

On September 14, 2015, Petitioner developed urinary retention issues, but the next day, Petitioner's abdominal pain and distention was improved. *Id.* at 253, 335-36. However, Petitioner developed difficulty standing and weakness in his lower extremities. *Id.* at 345.

Petitioner was seen by a consulting cardiologist, Scott Fertels, D.O., on September 15, 2015. Ex. 7 at 340. He was noted to be stable from a cardiological standpoint, as his ECG was normal. *Id.*

On September 16, 2015, Robert Sammartino, D.O. saw Petitioner in a neurology consult. Ex. 7 at 342-43. Dr. Sammartino noted that Petitioner's exam was suggestive of neuropathy and recommended MRIs of his brain and cervical spine. *Id.* at 342. The next day, Petitioner underwent a nerve conduction study (NCS) which revealed mild prolongation and distal motor latency, that did "not explain [Petitioner's] current clinical picture." *Id.* at 371.

Petitioner was seen by George Knod, D.O., a physical medicine and rehabilitation ("PM&R") specialist, on September 17, 2015. Ex. 7 at 344-47. Dr. Knod noted that Petitioner had received a pneumonia vaccine two weeks prior and had no viral prodrome. *Id.* at 345. Dr. Knod's impression was that Petitioner had an acute onset of paresthesias of the upper and lower extremities with significant dysmetria with possibly underlying neurogenic bowel and bladder. *Id.*at 346.

On September 18, 2015, Petitioner was seen by Dr. Vibbert, a neurocritical care specialist, who noted Petitioner's weakness had progressed so that he was unable to walk and stand. Ex. 7 at 348-50. Dr. Vibbert stated that prior examiners found Petitioner to have diminished reflexes. *Id.* at 349. Dr. Vibbert believed Petitioner had the Miller-Fisher variant of GBS and recommended he

start IVIG and additional testing for GQ1b antibodies titers to confirm the Miller-Fisher variant. *Id.* Dr. Vibbert noted that Petitioner was experiencing respiratory symptoms which required respiratory monitoring. *Id.* Petitioner was intubated later that night. *Id.* at 350.

On September 22, 2015, Petitioner was seen by Dr. Fred Rincon for a telemedicine neurocritical care evaluation. Ex. 7 at 357. Dr. Rincon opined that Petitioner had an acute demyelinating polyneuropathy and/or a Miller-Fisher variant, but believed the differential diagnoses should still include myasthenia gravis, Eaton Lambert syndrome, and anaplastic diseases. *Id.*

Petitioner was next seen for a consultation with Brian Beluch, D.O., an endocrinologist, for hypotension and weakness on September 30, 2015. Ex. 7 at 358-60. Dr. Beluch noted that Petitioner was initially admitted for stomach and abdominal pain associated with a small bowel obstruction or gastroenteritis. *Id.* at 358. Dr. Beluch noted Petitioner had a tracheostomy and a PEG tube placed because he was too weak to eat. *Id.*

On October 2, 2015, Petitioner was discharged from Kennedy Health System to Our Lady of Lourdes LTAC. Ex. 7 at 211-13. Petitioner remained at Our Lady of Lourdes from October 2, 2015 to October 29, 2015. *See generally* Ex. 6.1, 6.2. Upon discharge, his records noted that he had been weaned off the respirator and was making good progress with physical therapy. Ex. 6.1 at 28-29. Petitioner was still dealing with weakness, and needed assistance with a rolling walker and supervision. Ex. 5 at 3-5.

C. Rehabilitation Post-Hospitalization

On December 2, 2015, Petitioner was discharged from Our Ladies of Lourdes, with a discharge note of chronic diarrhea, and a viral infection during his stay. Ex. 4 at 69. Petitioner continued treatment with his PCP after his discharge from December 2, 2015 to January 2, 2016. Ex. 2, 3.

On December 31, 2015, Petitioner saw his cardiologist. Ex. 3 at 386-87. The record documented that Petitioner was able to eat on his own and his PEG tube and tracheostomy were discontinued. *Id.* He had lost weight and was now off all diabetes medications. *Id.* Petitioner was receiving physical therapy and making good progress, but was still unsteady and weak. *Id.*

On January 28, 2016, Petitioner had an initial evaluation with outpatient physical therapy. Ex. 3 at 41-43. His assessment included an inability to perform independent activities of daily living ("ADLs"). *Id.* at 42. Petitioner's physical therapy was planned for eight weeks to assist with strength and mobility. *Id.* at 43.

On February 9, 2016, Petitioner received results from an MRI of his right wrist, which showed tenosynovitis of the fourth extensor tendon compartment, and unremarkable median nerve and carpal tunnel. Ex. 3 at 97.

On March 28, 2016, Petitioner was seen by podiatry for thickened, enlarged nails in both feet that were causing pain and limiting ambulation. Ex. 3 at 385. There, it was noted that

Petitioner's "muscle strength and range of motion [were] adequate and consistent with the patient's age and generalized condition." *Id.*

On April 11, 2016, Petitioner was seen by Larry Janoff, D.O., a neurologist, who assessed Petitioner's complaints of pain at the wrists, tingling in the extremities, and a sense of swelling in his hands. Ex. 3 at 382-84. Upon examination, he had normal extraocular muscle movement, normal speech, and mild diminished hearing. *Id.* at 383. He was also ambulating without assistance. *Id.* The sensory exam showed a stocking type of diminished sensation in the lower extremities, and Petitioner had positive Tinel's sign[3] at the bilateral wrists. *Id.* Deep tendon reflexes were absent. *Id.* Dr. Janoff's impression was that petitioner had "GBS or one of the variants such as Miller-Fisher syndrome." *Id.* at 384. He planned to review records of prior diagnostic testing to decide whether to order an EMG. *Id.*

On April 29, 2016, Dr. Janoff followed up with a letter to Petitioner's PCP stating that Petitioner was complaining of heaviness in his hands and feet with needle-like sensation, and a separate pain in his right wrist at his last visit. Ex. 2 at 12; Ex. 3 at 380. Our Lady of Lourdes rehabilitation center was helpful in confirming Petitioner's GBS, and Dr. Janoff opined that his issues related to residuals of GBS and possibly his diabetes, in addition to a separate carpal tunnel syndrome in the right wrist. Ex. 2 at 12; Ex. 3 at 380. He suggested an EMG and a referral to a hand surgeon. Ex. 2 at 12; Ex. 3 at 380.

On June 13, 2016, an EMG/NCS showed mild right carpal tunnel syndrome. Ex. 2 at 16-18. There was no clear evidence of a demyelinating condition involving the right upper extremity based on the EMG study. *Id.* However, there was significant artifact throughout the study so it could not obtain a solid baseline, and an additional study was recommended if symptoms continued. *Id*. at 18.

D. Physical and Occupational Therapy Visits

On June 14, 2016, Petitioner began outpatient physical therapy treatment with the Gloucester County VA Center. Ex. 4 at 60. He reported numbness in his hands and feet and felt as if he was walking on glass. *Id.* He also complained of hand pain and stiffness. *Id.* Petitioner continued physical therapy with the Gloucester County VA Center until April 18, 2018. *Id.* at 22. Petitioner also began receiving occupational therapy services at Advanced Physical Therapy beginning on August 21, 2016. Ex. 3 at 2. Petitioner continued regular occupational therapy with Advanced Physical Therapy until June 17, 2019. Ex. 16 at 178.

During Petitioner's initial PT visit for GBS sequala, he complained of lower extremity pain and fatigue; the provider noted "GBS onset in Sep 2015 week prior to onset had a super pneumonia injection." Ex. 16 at 243.

[3] Tinel sign: "a tingling sensation in the distal end of a limb when percussion is made over the site of a divided nerve. It indicates a partial lesion or the beginning regeneration of the nerve." DORLAND'S MEDICAL DICTIONARY ONLINE, www.dorlandsonline.com/dorland/definition?id=106510 (last visited July 18, 2024).

On January 12, 2017, Petitioner saw rheumatologist, Dr. Richa Mishra, M.D. Ex. 3 at 376-77. In a consult letter to Petitioner's PCP, Dr. Mishra noted that Petitioner's previous lumbar puncture was negative, and the EMG showed no demyelinating disease. *Id.* His muscle weakness had been stable and had not worsened since 2015. *Id.* Petitioner complained of occasional tingling in his hands and feet and pain in the ankles and legs. *Id.* Dr. Mishra also documented that in September 2015, Petitioner had a pneumonia vaccine followed by weakness all over, which led to hospitalization. *Id.* As per his wife, it "lasted for 80 days and [he] was diagnosed with neuropathy of unclear etiology." *Id.* Dr. Mishra recommended an EMG to rule out radiculopathy/neuropathy/myopathy. *Id.* at 377. She also recommended a muscle biopsy to rule out inclusion body myositis/polymyositis/dermatomyositis. *Id.* In her assessment, Dr. Mishra noted that Petitioner had idiopathic peripheral autonomic neuropathy; a sudoscan was normal and revealed no evidence of small fiber neuropathy. *Id.* at 375. She also noted the most recent EMG showed mild right carpal tunnel syndrome. *Id.* at 372. However, the underlying C6-C7 right cervical radiculopathy could not be ruled out and there was no clear evidence of a demyelinating disease. *Id.* at 373.

On January 26, 2017, Petitioner once again saw Dr. Mishra. Ex. 3 at 371-72. All lab results for connective tissue disease were negative except for a mildly elevated sedimentation rate, and slightly high Smith antigen, which was to be repeated in three-to-four weeks. *Id.* Dr. Mishra's diagnoses were muscle weakness, osteoarthritis of knee, ankle and shoulder pain, and right shoulder tendinitis. *Id.*

A follow up appointment with Dr. Mishra on February 24, 2017, found all connective tissue disease labs were negative or normal. Ex. 3 at 368-69. There was no evidence of lupus or systemic connective tissue disease. An x-ray revealed degenerative joint disease in the spine as well as the sacroiliac joint. Petitioner was placed on gabapentin and NSAIDS. *Id.*

On February 27, 2017, Petitioner was seen by his PCP, Dr. Cogan. Ex. 3 at 240-44. Upon physical examination, he had a normal gait, normal strength, and normal reflexes. *Id.* at 241. Dr. Cogan noted that Petitioner may have some post-GBS neuropathy. *Id.* at 243.

On March 21, 2017, Petitioner was seen at the VA Center for a follow-up of his chronic conditions, including chest pain/palpitations, osteoarthritis, shoulder pain, and GBS. Ex. 4 at 44-46. He had peripheral neuropathy and generalized weakness though positive monofilament sensation in both feet. *Id.* He requested a referral for aqua therapy. *Id.*

On April 17, 2017, Petitioner was seen in occupational therapy. Ex. 3 at 2. The progress note stated: "GBS onset in Sept 2015 week prior to onset had a super pneumonia injection." *Id.* Petitioner's complaints included bilateral hand weakness and incoordination, and constant pain in the wrists. *Id.*

On May 9, 2017, Petitioner was seen by his PCP, Dr. Cogan. Ex. 3 at 234-39. He was unhappy with Dr. Janoff and frustrated with his visits with specialists; Dr. Cogan advised him to continue his medications, perform a home exercise program, get a second opinion from another neurologist, and follow-up in three months. *Id.* at 234, 239. During this visit, Petitioner remarked

that his strength was "remarkably well." *Id.* at 236. Dr. Cogan noted that Petitioner seemed to be stable, and he had full use of his hands. *Id.*

Discharge notes from Petitioner's June 27, 2017 occupational therapy visit indicated Petitioner's grip, pinch, and dexterity had increased. Ex. 10 at 22-24. GBS onset was listed as September 2015 after a "super pneumonia injection." *Id.* at 22. It was also noted that occupational therapy would end after Petitioner's thirty-seventh visit due to co-pay concerns. *Id.*

On February 5, 2018, Petitioner followed up with his VA physician, Dr. Soni, who noted a history of GBS "[status-post] inj[ection] 9/15 with peripheral neuropathy and generalized weakness." Ex. 12 at 130. On April 18, 2018, Petitioner returned to Dr. Soni, who repeated the same notation regarding GBS. Ex. 12 at 79.

On May 29, 2018, Petitioner visited neurologist Mayank Mathur, M.D., who noted Petitioner's diagnosis as GBS with residual pain and recommended an EMG. Ex. 17 at 2-4.

Advanced Physical Therapy records from June 26, 2018, indicate they discharged Petitioner because he never returned to PT after his November 11, 2017 visit. Ex. 16 at 2.

On September 11, 2018, Petitioner returned to Dr. Mathur to discuss his recent EMG results, which revealed a moderate axonal sensorimotor neuropathy. Ex. 10 at 103-05. At this visit, Petitioner complained of continued worsening lower extremity paresthesias. *Id.* at 103. Examination revealed reduced vibration and pinprick sensation in his fingers and toes and diminished reflexes. *Id.* at 104. As a result, Petitioner's gabapentin was increased. *Id.* at 105.

On September 18, 2018, Petitioner visited rheumatologist Alicia Weeks, M.D. Petitioner described the pain as constant stabbing/tingling pain from his shoulders to his fingers and knees to his feet. Ex. 10 at 98-100. Dr. Weeks explained that GBS was outside the scope of her practice and recommended a follow up with neurologist Steven Bromley, M.D. *Id.* at 98.

Petitioner saw Dr. Bromley in a neurology consultation on September 27, 2018. Ex. 10 at 16. Dr. Bromley noted that Petitioner presented with three years of ongoing problems related to polyneuropathy. *Id.* Dr. Bromley opined that a more appropriate diagnosis for Petitioner may be chronic inflammatory demyelinating polyneuropathy. *Id.* Dr. Bromley recommended Petitioner undergo a second round of IVIG with monthly booster doses. *Id.*

On February 13, 2019, Petitioner visited Dr. Bromley and was treated with IVIG. Ex. 13 at 2-4. Dr. Bromley noted continued neuropathic pain, unsteadiness, and leg spasms. *Id.* The plan was monthly IVIG and an increase in gabapentin. *Id.*

Petitioner visited Steven Scherer, M.D., at the University of Pennsylvania Neuromuscular Department, on March 4, 2020. Dr. Scherer confirmed a GBS diagnosis. Ex. 23 at 12. Dr. Scherer specifically noted that there is "no plausible alternative explanation for an acute paralytic illness," besides GBS. *Id.* at 14.

No additional medical records pertinent to this decision have been filed.

III. Expert Opinions and Qualifications

A. Petitioner's expert: Dr. Lawrence Steinman

Dr. Lawrence Steinman authored three expert report and testified at the entitlement hearing. *See* Ex. 24 (hereinafter "First Steinman Rep."); Ex. 59 (hereinafter "Second Steinman Rep."); Ex. 70 (hereinafter "Third Steinman Rep.").

1. Qualifications

Dr. Steinman attended Dartmouth College and Harvard Medical School. Ex. 83 (hereinafter "Steinman CV") at 1. Dr. Steinman completed his residency at Stanford and a neuroimmunology fellowship at the Weizmann Institute in Israel. Steinman CV at 1. Dr. Steinman is board certified in neurology. *Id.* at 2. He has taught neurology, pediatrics, and genetics since 1980 and is currently a professor at Stanford University in the departments of neurology, pediatrics, and genetics; he is also the George A. Zimmermann Professor of Neurological Sciences at Stanford University. *Id.* at 1. Dr. Steinman has approximately 50 patents and has published approximately 600 peer-reviewed papers. *Id.* at 2-48; Tr. at 64. Dr. Steinman was elected to the National Academy of Medicine and National Academy of Science. Tr. at 10. I recognized him as an expert in neurology, neuroimmunology, and demyelinating disorders. *Id.* at 14-15.

2. Expert Opinion

Dr. Steinman testified during both days of the entitlement hearing held on March 29-30, 2023, and recapped the opinions outlined in his expert reports.

Dr. Steinman emphasized that GBS is often associated with Campylobacter jejuni ("*c. jejuni*"), but that is not always the case. Tr. at 31. *C. jejuni* expresses a lipopolysaccharide structure similar to the carbohydrate epitopes in sialic acid containing glycolipids and gangliosides. *Id.* at 30. One piece of literature showed that glycolipids were antigens for circulating autoantibodies in autoimmune processes affecting the nervous system, like neuropathies associated with immunoglobulin M, such as GBS. *Id.* Fredman, *The Role of Antiglycolipid Antibodies In Neurological Disorders*, ANNALS N.Y. ACAD. SCI. 341, 348-49 (1998) (filed as Ex. J, Tab 3) (hereinafter "Fredman"). Infections with the Epstein-Barr virus ("EBV") account for approximately ten percent of GBS cases, and are associated with contactin-1 and contactin-2. Lanz et al., *Roadmap For Understanding Mechanisms on How Epstein–Barr Virus Triggers Multiple Sclerosis and for Translating These Discoveries in Clinical Trials*, 12 CLINICAL & TRANSLATIONAL IMMUNOLOGY 1, 3 (2023) (filed as Ex. 85) (hereinafter "Lanz") at 3; Tr. at 33-34. Gangliosides, Dr. Steinman opined, can also be a target antigen in GBS cases. Tr. at 34. This was particularly relevant at the node of Ranvier where proteins are targeted in GBS; the GlialCAM molecule has "remarkable" homology with proteins at this location. Kanter et al., *Lipid Microarrays Identify Key Mediators of Autoimmune Brain Inflammation*, 12 NATURE MED. 138, 138, n. 10 (2006) (filed as Ex. 34) (hereinafter "Kanter"); Tr. at 32.

Dr. Steinman also opined that vaccines can cause GBS. Tr. at 35. Dr. Steinman used case reports to support his position that the Prevnar 13 vaccine can cause GBS. Tr. at 36. One case report associated bacteremic pneumococcus pneumoniae infection with GBS. *Id.* at 36-37; Bianchi & Domenighetti, *Pneumococcus Pneumoniae Infection and Guillain-Barre Syndrome: Fortuitous or Specific Association?*, 32 INTENSIVE CARE MED. (2006) (filed as Ex. 87) (hereinafter "Bianchi"). Another case report identified an individual who developed pneumococcus and went on to develop GBS. White et al., *A Novel Pneumococcus With a New Association*, 9 TRAVEL MED. & INFECTIOUS DISEASES 1, 6-7 (2011) (filed as Ex. 69). Haber et al. discussed the effectiveness and safety of the Prevnar 13 vaccine, but did verify 11 GBS reports with symptom onset within 42 days. Haber 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 6330, 6334 (2016) (filed as Ex. 60) (hereinafter "Haber"); Tr. at 37. Some articles saw less of a signal, such as Tseng and Baxter, but they could not exclude the possible association. Tseng et al., *Pneumococcal Conjugate Vaccine Safety in Elderly Adults*, OPEN FORUM INFECTIOUS DISEASES 1, 6 (2018) (filed as Ex. 56) (hereinafter "Tseng"); Baxter et al., *Lack of Association of Guillain-Barre Syndrome with Vaccinations*, 57 CLINICAL INFECTION DISEASES 197, 202-03 (2013) (filed as Ex. 57) (hereinafter "Baxter"); Tr. at 39-41. In summary, Dr. Steinman found that these studies do not indicate that one could not get GBS from a vaccine. Tr. at 42.

Dr. Steinman cited his two major theories, both based on molecular mimicry, to show how the Prevnar 13 vaccine can cause GBS. Tr. 42. Dr. Steinman contends that molecular mimicry, according to cited literature, is a common mechanism for vaccine-based injuries. Second Steinman Rep. at 25 (*citing* Fujinami & Oldstone, *Amino Acid Homology Between the Encepbalitogenic Site of Myelin Bmic Protein and Virus: Mechanism for Autoimmunity*, 230 SCIENCE 1043, 1043 (1985) (filed as Ex. 89) (hereinafter "Fujinami")); Tr. at 16, 19-21. He opined that molecular mimicry does not need to be exact to cause a reaction, but only requires a certain degree of homology in the amino acid chain. First Steinman Rep. at 15 (*citing* Fujinami at 1043; Gautam et al., *A Polyalanine Peptide with Only Five Native Myelin Basic Protein Residues Induces Autoimmune Encephalomyelitis*, 176 J. EXPERIMENTAL MED. 605, 605 (1992) (filed as Ex. 44); Gautam et al., *Minimum Structural Requirements for Peptide Presentation by Major Histocompatibility Complex Class II Molecules: Implications in Induction of Autoimmunity*, 91 IMMUNOLOGY 767, 767 (1994) (filed as Ex. 45); Gautam et al., *A Viral Peptide with Limited Homology to a Self Peptide Can Induce Clinical Signs of Experimental Autoimmune Encephalomyelitis*, 161 J. IMMUNOLOGY 60, 60 (1998) (filed as Ex. 46) (hereinafter the "Gautam Articles"); Tr. at 21-26.

Though most of the literature he cited to support a theory of molecular mimicry relates to different vaccines, he found that this theory was also relevant to the pathogenesis of GBS. Third Steinman Rep. at 12; Fujinami at 1043; Lanz at 3; Tr. at 25-27. Dr. Steinman cited to Kantor, which found that "[a]utoimmune responses directed against phospholipids and gangliosides *contribute* to the pathogenesis in systemic lupus erythematosus and Guillain-Barre syndrome, respectively." Kanter at 138 (emphasis added); Tr. at 29. However, Dr. Steinman argued that gangliosides are not the only target antigens in GBS. Tr. at 31.

Petitioner's first causal theory relates to 18C and 23F, which are two sugars in the Prevnar 13 vaccine[4] that Dr. Steinman contends cross-react with an element of the human body. First Steinman Rep. at 7-8; *Prevnar 13 Package Insert* (filed as Ex. 30), at 24 (hereinafter "Prevnar 13 Package Insert"); Emini et al., *United States Patent* (2022) (filed as Ex. 31), at 34 (hereinafter "Prevnar 13 Patent") (listing saccharides including 18 and 23); Tr. at 42-44. The phosphate head group[5] often found on phosphoglycerol, is in many molecules in the body; it is electrically charged and can be a target of the immune response in both multiple sclerosis (hereinafter "MS") and GBS. Tr. at 44. Phosphoglycerol is essential for the immunogenicity of 18C. *Id*. at 47-49, 54, 63-68; Prevnar 13 Patent at 34; Nakos et al., *Anti-Phospholipid Antibodies in Serum from Patients with Guillain-Barre Syndrome*, INTENSIVE CARE MED. 1401, 1401-02 (2005) (filed as Ex. 33) (hereinafter "Nakos"); Chang et al., *Relevance Of O-Acetyl and Phosphoglycerol Groups for the Antigenicity of Streptococcus Pneumoniae Serotype 18C Capsular Polysaccharide*, 30 VACCINE 7090, 7091 (2012) (filed as Ex. 37) (hereinafter "Chang"); Mata et al., *Anti-GM1, Anti-Central Myelin Proteins, and Anti-Cardiolipin Autoantibodies During Plasma-Exchange in Guillain-Barre Syndrome (GBS)*, 13 J. CLINICAL APHERESIS 155, 158-89 (1998) (filed as Ex. 93).

Dr. Steinman cited medical literature about MS to support his theory with respect to GBS. Tr. at 55. He opined this literature is still a helpful indicator for GBS because one of the constant features of antibody binding to myelin is recognition of the phosphate head group on phosphoglycerol. First Steinman Rep. at 10; *see e.g.*, Chang at 7095; Lugowski & Jennings, *Structural Determination Of The Capsular Polysaccharide of Streptococcus Pneumoniae Type 18C (56)*, CARBOHYDRATE RES. 131, 131 (1984) (filed as Ex. 38); Barber et al., *Binding of Phenylphosphocholine-Carrier Conjugates to the Combining Site of Antibodies Maintains a Conformation of the Hapten*, 35 BIOCHEMISTRY 2958, 2958 (1996) (filed as Ex. 63) (hereinafter "Barber"); Ho et al., *Identification of Naturally Occurring Fatty Acids of the Myelin Sheath That Resolve Neuroinflammation*, 4 SCI. TRANSLATIONAL MED. 1, 1 (2012) (filed as Ex. 90) ("hereinafter Ho"); Tr. at 59-63.

Dr. Steinman also cited to literature involving other vaccines like the Pneumovax 23 vaccine; he found this literature helpful because both vaccines contain the 23F sugar. Second Steinman Rep. at 13; Third Steinman Rep. at 8; *see e.g.*, Bryson et al., *Structures of Preferred Human IgV Genes-Based Protective Antibodies Identify How Conserved Residues Contact Diverse Antigens and Assign Source of Specificity to CDR3 Loop Variation*, 196 J. IMMUNOLOGY 4723, 4725–26 (2016) (filed as Ex. 65) (hereinafter "Bryson"); Tr. at 54-57.

Petitioner's second theory focuses on the molecular mimic between the carrier protein CRM_{197}[6] and contactin-1.[7] First Steinman Rep. at 15; Tr. at 71. Dr. Steinman opined that when a

[4] The Prevnar 13 vaccine is composed of 13 streptococcus pneumonia serotypes. Tr. at 43, 50.

[5] A phosphate head group is also known as a polar head group. Tr. at 45.

[6] CRM_{197} is also known as cross-reacting material number 197, which differs from diphtheria toxin by one amino acid. Tr. at 72.

[7] Contactin-1 is a paranodal protein at the node of Ranvier Tr. at 73. The node of Ranvier is an axon of the nerve where there is no myelin. Tr. at 72.

molecular mimic occurs, the antibodies to some of the proteins can wreck the structure at the node of Ranvier and block sodium and potassium channels, which could lead to dysautonomia or sensory loss in GBS. Fehmi et al., *Nodes, Paranodes, and Neuropathies*, 89 J. NEUROLOGY, NEUROSURGERY, & PSYCHIATRY 61, 62, 64 (2018) (filed as Ex. 41); Tr. at 75-76. He cited to another animal study by Devaux, which found contactin-1, among other paranodal proteins, are novel target antigens in GBS. Devaux et al., *Nodal Proteins are Target Antigens in Guillain-Barre Syndrome*, 17 J. PERIPHERAL NERVOUS SYSTEM 62, 66-69 (2012) (filed as Ex. 84); Tr. at 76-79, 81.

Dr. Steinman used a three-step process to assess molecular mimics between the Prevnar 13 vaccine and contactin-1. First Steinman Rep. at 17, 19; Tr. at 79. He began with a BLAST search and found a sequence of five out of ten identical amino acids. First Steinman Rep. at 19; Tr. at 81. Next, he determined, based on the Gautam papers, that these sequences could cause disease, even if they were not exact. First Steinman Rep. at 20; Tr. at 80-82. Finally, he analyzed whether other researchers had described this area of similarity in the Immune Epitope Database ("IEDB"). Tr. at 82. There, he discovered that another paper found a region around WEQ where there was an immune response when a human was immunized with diphtheria. *Id*. at 82-83; Second Steinman Rep. at 20 (*citing* Raju et al., *Epitopes for Human CD4+ Cells on Diphtheria Toxin: Structural Features of Sequence Segments Forming Epitopes Recognized by Most Subjects*, 25 EUR. J. IMMUNOLOGY 3207, 3207 (1995) (filed as Ex. 66). Dr. Steinman opined that this filter funnel process was supportive of his second theory.[8]

Further, Dr. Steinman believed that the Prevnar 13 vaccine Petitioner received did cause him to develop GBS. First Steinman Rep. at 25; Second Steinman Rep. at 30; Third Steinman Rep. at 32. Dr. Steinman ruled out any evidence of a prior infection and Petitioner's doctors continuously found that the etiology of Petitioner's GBS was unknown. Ex. 7 at 288, 306, 355; Tr. at 114-15, 121-22. No doctor in the hospital diagnosed Petitioner with a GI infection, no stool samples were taken to identify a gastrointestinal infection, and Petitioner did not receive treatment for a GI infection. Ex. 6.1 at 35; Tr. at 115-16. Petitioner also never reported any fever, diarrhea, or vomiting initially. Ex. 7 at 174, 227, 333; Tr. at 111, 115, 122. Thus, since there was no known infection, this was an occasion where GBS presented with autonomic dysfunction and ileus.[9] Ex. 6.1 at 36; Ex. 7 at 346; Tr. at 113, 116-17. Although an unusual presentation, Dr. Steinman pointed to literature which described other individuals presenting with ileus and abdominal pain prior to symptoms of GBS. Chakraborty et al., *Dysautonomia in Guillain–Barré Syndrome: Prevalence, Clinical Spectrum, and Outcomes*, 32 NEUROCRITICAL CARE SOC'Y 113, 113-14 (2020) (filed as Ex. 98); Lee et al., *Paralytic Ileus as the Presenting Symptom For Guillain–Barre Syndrome: A Case Report*, 48 J. INT'L MED. RES. 1, 1 (2019) (filed as Ex. 99); Liu et al., *Paralytic Ileus as First Symptom of Miller Fisher Syndrome: A Case Report*, 101 MED. 1, 1 (2022) (filed as Ex. 100); Tr. at 117-20.

[8] Though discussed minimally, Dr. Steinman addressed a third theory based on the vaccine's alum adjuvant. Tr. at 85-86; First Steinman Rep. at 22-23. Petitioner indicated his intent to abandon that theory at the entitlement hearing, so I have not summarized it or analyzed it in this decision. Tr. at 392.

[9] Dr. Steinman defined ileus as when the bowels don't move along normally. Tr. at 94.

Dr. Steinman opined that the timing of onset of Petitioner's GBS was consistent with the epidemiologic studies in Schonberger, noting that up to 42 days after vaccination is medically appropriate for a vaccine-induced immune response. First Steinman Rep. at 4 (*citing* Schonberger et al., *Guillain-Barre Syndrome Following Vaccination In The National Influenza Immunization Program, United States, 1976-1977*, 110 AMERICAN JOURNAL OF EPIDEMIOLOGY 2, 105-23 (1979) (filed as Ex. 58); Stratton et al., Committee to Review Adverse Effects of Vaccines, Institute of Medicine, eds., *Adverse Effects of Vaccines: Evidence and Causality*, Washington (DC): National Academies Press (2012) (not filed as an exhibit); Tr. at 121. Dr. Steinman originally found that Petitioner's GBS began the evening of September 15, 2015, with difficulty standing, but during the hearing he testified that an earlier timeframe of September 10, 2015, was accurate because that was the beginning of Petitioner's ileus. *Id.* at 113-14, 122; First Steinman Rep. at 4; Ex. 7 at 172. Regardless of the few days difference, Dr. Steinman opined that this onset was within a medically appropriate temporal interval. First Steinman Rep. at 25 (*citing see, e.g.*, Baxter at 199-202; Tseng at 2; Haber at 6333-34); Tr. at 121-25.

B. Respondent's expert: Dr. J. Lindsay Whitton

Dr. Whitton authored three expert report and testified at the entitlement hearing. *See* Ex. A (hereinafter "First Whitton Rep."); Ex. F (hereinafter "Second Whitton Rep."); Ex. I (hereinafter "Third Whitton Rep.").

1. Qualifications

Dr. Whitton received his M.B., Ch.B. and Ph.D. from the University of Glasgow, Scotland. Ex. C (hereinafter "Whitton CV") at 1. Dr. Whitton was a professor in the Department of Immunology and Microbial Science at the Scripps Research Institute. *Id.* He has since retired and holds a position of emeritus professor at Scripps. Tr. at 269. Dr. Whitton is a member of a number of professional societies, including the American Association of Pathologists, American Associates of Immunologists, and the American Society of Virology. Whitton CV at 1. Dr. Whitton is also on the editorial boards of scientific journals and has published nearly 200 papers. *See id.* at 1, 2-14. I recognized him as an expert in immunology. Tr. at 279.

2. Expert Opinion

Dr. Whitton began his testimony by discussing the formulation of the Prevnar 13 vaccine and its CRM_{197} component. Tr. at 278. Dr. Whitton explained that streptococcus pneumoniae, which the Prevnar 13 vaccine protects against, has not been associated with GBS, unlike the flu virus. *Id.* at 281-82. The theorized mechanism of how *c. jejuni* can cause GBS is through lipooligosaccharides ("LOS") and gangliosides on human nerve cells. *Id.* at 283-85. *S. pneumoniae* is not known to be a trigger of GBS, and if the bacteria is not known to cause the disease it is difficult to understand how the vaccine could do so. *Id.* at 285-86. Dr. Whitton further elaborated that *c. jejuni* is a gram negative bacteria whereas *s. pneumoniae* is a gram positive bacteria that does not express LOS. First Whitton Rep. at 9. So while *c. jejuni* may cause GBS through molecular mimicry, *s. pneumoniae* does not have the same structure that *c. jejuni* does. *Id.*

The Prevnar 13 vaccine is conjugated from the diphtheria toxin, which is forms the CRM_{197} protein in the vaccine. Tr. at 290. Dr. Whitton elaborated that CRM_{197} was created because children were not responding well to unconjugated polysaccharides. *Id.* It is a safe vaccine for children and has been used in adult vaccines as well. *Id.* at 291. This is relevant to Dr. Steinman's theory of molecular mimicry between CRM_{197} and contactin 1. *Id.* at 291-92. There are approximately 100 strains of the pneumococcus bacteria; the Prevnar 13 vaccine contains 13 different strains of the bacteria. First Whitton Rep. at 3.

The Haber paper concluded that there was no increased risk of developing GBS after receiving either the Prevnar 13 or the Pneumovax vaccines. *Id.* at 293. Furthermore, while molecular mimicry is a valid mechanism, it has not been proven to be a "frequent cause of human disease." *Id.* at 297.

Regarding Dr. Steinman's theory about polysaccharides, Dr. Whitton stated that polysaccharides can vary vastly in structure. Tr. at 287-88. There are about 12 different monosaccharides that can combine in various positions and angles, to form large molecules. First Whitton Rep. at 4. Polysaccharides are unlike amino acid sequences, which combine linearly in a long chain, and this contributes to the diversity of the structure of polysaccharides. *Id.* at 4. This is significant because Dr. Whitton opined that the antibodies would likely bind to only one of the 13 strains of the Prevnar 13 vaccine components. *Id*. at 5-6.

For molecular mimicry to occur, Dr. Whitton explained three things need to happen: 1) the vaccine material must induce an immune response; 2) the reaction induced by the vaccine must cross react with shared host material; and 3) the cross-reactive response must be harmful. First Whitton Rep. at 12.

Dr. Whitton provided a summary of Dr. Steinman's phosphoglycerol theory, which is as follows: some pneumococcal polysaccharides have a phosphoglycerol molecule that induces an antibody response that recognizes phosphoglycerol. *Id.* at 301. Some of the phospholipids that are relevant are phosphatidylserine ("PS"), phosphatydylicholine ("PC"), and phosphotidylethanol ("PE"). *Id.* at 302. These phospholipids are located on the myelin sheath, which hypothetical antibodies attack, triggering GBS. *Id.* Furthermore, Dr. Whitton stated that PC, PS, and PE do not contain phosphoglycerol. Tr. at 312.

Dr. Whitton opined about the various gaps in Dr. Steinman's phosphoglycerol theory. Dr. Whitton stated the Bryson paper does not demonstrate that antibodies recognize phosphoglycerol by itself, but instead recognize phosphoglycerol plus part of the bacterial sugar. Tr. at 306. Furthermore, Dr. Steinman's citation to the Gilburd and Nakos papers does not demonstrate that the phospholipid antibodies were disease causing; Gilburd specifically states that "these autoantibodies are probably produced as a result of the myelin damage rather than cause the demyelination." First Whitton Rep. at 14; Gilburd at 1.

Dr. Steinman's other medical literature citations were unpersuasive to Dr. Whitton as they focused on MS, which involves the central nervous system, as opposed to GBS which involves the peripheral nervous system. First Whitton Rep. at 14-15. Dr. Steinman's phosphoglycerol theory involves antibodies attacking specific polar heads on nerve cells, however the leading targets in

GBS are gangliosides, which "generally do not contain polar head groups." *Id.* at 15. Dr. Whitton also provided a visual example of the difference between sphingomyelin, a polar head group, and a ganglioside in his report. *Id.* at 28.

Dr. Whitton contested the significance of Dr. Steinman's BLAST searches and filtration process. He highlighted that Dr. Steinman's e-value was not significant because it was so high. Second Whitton Rep. at 11. The e-values were too high and demonstrate that the homologies were a result of chance, and not because of significant or meaningful mimics found. *Id.* at 10-11. Dr. Whitton also stated that the IEDB results do not demonstrate the significance of the sequence or that the sequence is immunogenic. *Id.* at 12-13.

C. Respondent's expert: Dr. Brian Callaghan

Dr. Callaghan authored two expert report and testified at the entitlement hearing. *See* Ex. C (hereinafter "First Callaghan Rep."); Ex. H (hereinafter "Second Callaghan Rep."). Much of Dr. Callaghan's opinion addressed the question of whether Petitioner had a GI illness before he developed GBS, or whether he had an ileus with no GI illness. Because I have decided this case on *Althen* prong one only, I do not summarize or analyze this portion of Dr. Callaghan's testimony.

1. Qualifications

Dr. Callaghan received his medical degree from the University of Pennsylvania in 2004. Ex. E (hereinafter "Callaghan CV") at 1. Dr. Callaghan completed his residency in neurology at the University of Pennsylvania and two fellowships at the University of Michigan. *Id.* Dr. Callaghan is board certified in neurology and electrodiagnostic medicine. *Id.* He is a professor at the University of Michigan, Ann Arbor and serves as a staff physician in the neurology department with the VA Ann Arbor Healthcare system. *Id.* Dr. Callaghan is also the director of the VA Ann Arbor Healthcare system's ALS Clinic. *Id.* at 1-2. Dr. Callaghan is actively involved in research and is a journal reviewer for an extensive number of publications including: Annals of Neurology, Brain, Brain and Behavior, Diabetes, Lancet, Neurology. *Id.* at 3-5. Dr. Callaghan has published over 70 peer reviewed papers and 3 book chapters. *Id.* at 10-14. I recognized him as an expert in neurology. Tr. at 182-83.

2. Expert Opinion

Dr. Callaghan opined that he agreed Petitioner's diagnosis was Miller Fisher syndrome, a variant of GBS. First Callaghan Rep. at 3. He confirmed that Petitioner had the triad of symptoms typically associated with Miller Fisher syndrome, which are eye movement abnormalities, diplopia, and a sensory ataxia and areflexia. Tr. at 183-84. Dr. Callaghan elaborated that Petitioner developed Miller Fisher syndrome 12 days after the Prevnar 13 vaccination. *Id.* Dr. Callaghan also noted that he disagreed with Dr. Bromley's diagnosis of CIDP because Petitioner's medical records supported a monophasic disease course, Petitioner's imaging did not support CIDP, nor did his lack of response to IVIG. *Id.*

Regarding the Prevnar 13 vaccination that Petitioner received, Dr. Callaghan stated that there was "no convincing evidence to support a likely association between Prevnar 13 vaccination and GBS". First Callaghan Rep. at 3.

Dr. Callaghan was critical of the medical literature presented by Dr. Steinman regarding how molecular mimicry between the Prevnar 13 vaccine could have caused Petitioner's GBS. Specifically, Dr. Callaghan noted that none of the medical literature cited by Dr. Steinman demonstrated that the phospholipids in the vaccine caused the demyelination in GBS. First Callaghan Rep. at 3-4. In Gilburd, the authors stated that phospholipid antibodies were likely produced as a result of myelin damage, and not the cause of demyelination. *Id.* at 4. Dr. Callaghan also identified contactin-1 as part of the pathogenesis of CIDP, and not GBS. *Id.*

Dr. Callaghan next addressed Dr. Steinman's theories of causation. He believed that there was one theory involving phospholipids, one with contactin, and one with the alum adjuvant. Tr. at 193. Dr. Callaghan opined that Dr. Steinman's theory involving phospholipids was confusing because he seemed to lump together glycolipids and phospholipids, which were also not known to be involved in the pathogenesis of GBS; additionally, at the yearly international meeting, ganglioside antibodies were seen in a "vast majority" of GBS patients and gangliosides are still believed to be a part of GBS pathogenesis. *Id.* Dr. Callaghan criticized Dr. Steinman's phospholipid theory for its lack of specificity. *Id.* at 194. There are many phosphate head groups in all sorts of molecules, and phosphoglycerols are not a part of GBS pathogenesis. *Id.*

Regarding Dr. Steinman's second theory involving contactin-1, Dr. Callaghan opined that contactin-1 is not known to be involved in GBS. Tr. at 195. Dr. Callaghan conceded that contactin-1 is a well-established cause of CIDP, including acute CIDP. *Id.* Most CIDP patients do not improve with IVIG; however Petitioner make a "remarkable recovery" with IVIG. *Id.* at 195-96. Dr. Callaghan clarified that CIDP and GBS are very different diseases, with different treatments and different presentations even though both are demyelinating conditions. *Id.* at 196.

As additional epidemiological evidence, Dr. Callaghan presented the Haber paper to demonstrate the incidence rate of GBS after a Prevnar 13 vaccine is lower that the incidence rate of GBS in the public without vaccination. Tr. at 199; *see* Haber at 6330–34. Dr. Callaghan opined there was no data to support Dr. Steinman's proposed mechanism and no epidemiological data to support that the Prevnar 13 vaccine could cause GBS. Tr. at 199.

IV. Applicable Law

A. Petitioner's Burden in Vaccine Program Cases

Under the Vaccine Act, a petitioner may prevail in one of two ways. First, a petitioner may demonstrate that a vaccinee suffered a "Table" injury—i.e., an injury listed on the Vaccine Injury Table that occurred within the time period provided in the Table. § 11(c)(1)(C)(i). "In such a case, causation is presumed." *Capizzano v. Sec'y of Health & Hum. Servs.*, 440 F.3d 1317, 1320 (Fed.

Cir. 2006); *see* § 13(a)(1)(B). Second, where the alleged injury is not listed in the Vaccine Injury Table, a petitioner may demonstrate that she suffered an "off-Table" injury. § 11(c)(1)(C)(ii).

For both Table and non-Table claims, Vaccine Program petitioners bear a "preponderance of the evidence" burden of proof. Section 13(1)(a). That is, a petitioner must offer evidence that leads the "trier of fact to believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the judge of the fact's existence." *Moberly v. Sec'y of Health & Hum. Servs.*, 592 F.3d 1315, 1324 (Fed. Cir. 2010); *see also Snowbank Enter. v. United States*, 6 Cl. Ct. 476, 486 (1984) (mere conjecture or speculation is insufficient under a preponderance standard). 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, a petitioner must demonstrate that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly*, 592 F.3d at 1321 (quoting *Shyface v. Sec'y of Health & Hum. Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999)); *Pafford v. Sec'y of Health & Hum. Servs.*, 451 F.3d 1352, 1355 (Fed. Cir. 2006). A petitioner may not receive a Vaccine Program award based solely on his assertions; rather, the petition must be supported by either medical records of by the opinion of a competent physician. Section 13(a)(1).

In attempting to establish entitlement to a Vaccine Program award of compensation for a non-Table claim, a petitioner must satisfy all three of the elements established by the Federal Circuit in *Althen v. Secretary of Health and Human Services*. 418 F.3d 1274 (Fed. Cir. 2005). *Althen* requires that petitioner establish by preponderant evidence that the vaccinations he received caused her injury "by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Id.* at 1278.

Each of the *Althen* prongs requires a different showing. Under *Althen* prong one, petitioner must provide a "reputable medical theory," demonstrating that the vaccine received *can cause* the type of injury alleged. *Pafford*, 451 F.3d at 1355-56 (citations omitted). To satisfy this prong, a petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Hum. Servs*., 35 F.3d 543, 548 (Fed. Cir. 1994). Such a theory must only be "legally probable, not medically or scientifically certain." *Id.* at 549.

Petitioner may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu v. Sec'y of Health & Hum. Servs.*, 569 F.3d 1367, 1378-79 (Fed. Cir. 2009) (citing *Capizzano*, 440 F.3d at 1325-26). Special Masters, despite their expertise, are not empowered by statute to conclusively resolve what are complex scientific and medical questions, and thus scientific evidence offered to establish *Althen* prong one is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Id.* at 1380. Accordingly, special masters must take care not to increase the burden placed on petitioners in offering a scientific theory linking vaccine to injury. *Contreras v. Sec'y of Health & Hum. Servs*., 121 Fed. Cl. 230, 245 (2015) ("[p]lausibility … in many cases may be enough to satisfy *Althen* prong one" (emphasis in original)), *vacated on other grounds*, 844 F.3d 1363 (Fed. Cir. 2017). But this does not negate or reduce a petitioner's ultimate burden to establish

her overall entitlement to damages by preponderant evIdence. *W.C. v. Sec'y of Health & Hum. Servs*., 704 F.3d 1352, 1356 (Fed. Cir. 2013) (citations omitted).

The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326 ("medical records and medical opinion testimony are favored in vaccine cases, as 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'") (quoting *Althen*, 418 F.3d at 1280). Medical records are generally viewed as particularly trustworthy evidence, because they are created contemporaneously with the treatment of the patient. *Cucuras v. Sec'y of Health & Hum. Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993).

However, medical records and/or statements of a treating physician's views do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. Section 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder v. Sec'y of Health & Hum. Servs*., 88 Fed. Cl. 706, 746 n.67 (2009) ("there is nothing … that mandates that the testimony of a treating physician is sacrosanct–- that it must be accepted in its entirety and cannot be rebutted"). As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases. The views of treating physicians should also be weighed against other, contrary evidence also present in the record -- including conflicting opinions among such individuals. *Hibbard v. Sec'y of Health & Hum. Servs*., 100 Fed. Cl. 742, 749 (2011) (not arbitrary or capricious for special master to weigh competing treating physicians' conclusions against each other), *aff'd*, 698 F.3d 1355 (Fed. Cir. 2012); *Caves v. Sec'y of Health & Hum. Servs*., No. 06-522V 2011 WL 1935813 at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011), *mot. for review den'd*, 100 Fed. Cl. 344, 356 (2011), *aff'd without opinion*, 475 Fed. App'x 765 (Fed. Cir. 2012).

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been 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 a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *Id.* at 1352; *Shapiro v. Sec'y of Health & Hum. Servs*., 101 Fed. Cl. 532, 542 (2011), *recons. denied after remand on other grounds*, 105 Fed. Cl. 353 (2012), *aff'd without op.,* 503 F. App'x 952 (Fed. Cir. 2013). *Koehn v. Sec'y of Health & Hum. Servs*., No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review den'd* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

B. Law Governing Analysis of Fact Evidence

The process for making factual determinations in Vaccine Program cases begins with analyzing the medical records, which are required to be filed with the petition. Section 11(c)(2). The special master is required to consider "all [] relevant medical and scientific evidence contained in the record," including "any diagnosis, conclusion, medical judgment, or autopsy or coroner's report which is contained in the record regarding the nature, causation, and aggravation of the petitioner's illness, disability, injury, condition, or death," as well as the "results of any diagnostic or evaluative test which are contained in the record and the summaries and conclusions." Section 13(b)(1)(A). The special master is then required to weigh the evidence presented, including contemporaneous medical records and testimony. *See Burns v. Sec'y of Health & Hum. Servs*., 3 F.3d 413, 417 (Fed. Cir. 1993) (it is within the special master's discretion to determine whether to afford greater weight to contemporaneous medical records than to other evidence, such as oral testimony surrounding the events in question that was given at a later date, provided that such determination is evidenced by a rational determination).

Medical records created contemporaneously with the events they describe are generally trustworthy because they "contain information supplied to or by health professionals to facilitate diagnosis and treatment of medical conditions," where "accuracy has an extra premium." *Kirby v. Sec'y of Health & Hum. Servs.*, 997 F.3d 1378 (Fed. Cir. 2021) citing *Cucuras*, 993 F.2d at 1528. This presumption is based on the linked proposition that (i) sick people visit medical professionals; (ii) sick people honestly report their health problems to those professionals; and (iii) medical professionals record what they are told or observe when examining their patients in as accurate a manner as possible, so that they are aware of enough relevant facts to make appropriate treatment decisions. *Sanchez v. Sec'y of Health & Hum. Servs.*, No. 11-685V, 2013 WL 1880825 at *2 (Fed. Cl. Spec. Mstr. Apr. 10, 2013) *mot. for rev. denied*, 142 Fed. Cl. 247, 251-52 (2019), *vacated on other grounds and remanded*, 809 Fed. Appx. 843 (Fed. Cir. Apr. 7, 2020).

Accordingly, if the medical records are clear, consistent, and complete, then they should be afforded substantial weight. *Lowrie v. Sec'y of Health & Hum. Servs.*, No. 03-1585V, 2005 WL 6117475 at *20 (Fed. Cl. Spec. Mstr. Dec. 12, 2005). Indeed, contemporaneous medical records are generally found to be deserving of greater evidentiary weight than oral testimony–- especially where such testimony conflicts with the record evidence. *Cucuras*, 993 F.2d at 1528; see also *Murphy v. Sec'y of Health & Hum. Servs.*, 23 Cl. Ct. 726, 733 (1991), *aff'd per curiam*, 968 F.2d 1226 (Fed. Cir. 1992), *cert. den'd*, *Murphy v. Sullivan*, 506 U.S. 974 (1992) (citing *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 396 (1947) ("[i]t has generally been held that oral testimony which is in conflict with contemporaneous documents is entitled to little evidentiary weight.")).

However, there are situations in which compelling oral testimony may be more persuasive than written records, such as where records are deemed to be incomplete or inaccurate. *Campbell v. Sec'y of Health & Hum. Servs.*, 69 Fed. Cl. 775, 779 (2006) ("like any norm based upon common sense and experience, this rule should not be treated as an absolute and must yield where the factual predicates for its application are weak or lacking"); *Lowrie*, 2005 WL 6117475 at *19 ("[w]ritten records which are, themselves, inconsistent, should be accorded less deference than those which are internally consistent") (quoting *Murphy*, 23 Cl. Ct. at 733)). Ultimately, a determination regarding a witness's credibility is needed when determining the weight that such testimony should

be afforded. *Andreu*, 569 F.3d at 1379; *Bradley v. Sec'y of Health & Hum. Servs.*, 991 F.2d 1570, 1575 (Fed. Cir. 1993).

When witness testimony is offered to overcome the presumption of accuracy afforded to contemporaneous medical records, such testimony must be "consistent, clear, cogent and compelling." *Sanchez*, 2013 WL 1880825 at *3 (citing *Blutstein v. Sec'y of Health & Hum. Servs.*, No. 90-2808V, 1998 WL 408611 at *5 (Fed. Cl. Spec. Mstr. June 30, 1998)). In determining the accuracy and completeness of medical records, the Court of Federal Claims has listed four possible explanations for inconsistencies between contemporaneously created medical records and later testimony: (1) a person's failure to recount to the medical professional everything that happened during the relevant time period; (2) the medical professional's failure to document everything reported to her or him; (3) a person's faulty recollection of the events when presenting testimony; or (4) a person's purposeful recounting of symptoms that did not exist. *LaLonde v. Sec'y of Health & Hum. Servs.*, 110 Fed. Cl. 184, 203-04 (2013), *aff'd*, 746 F.3d 1334 (Fed. Cir. 2014). In making a determination regarding whether to afford greater weight to contemporaneous medical records or other evidence, such as testimony at hearing, there must be evidence that this decision was the result of a rational determination. *Burns*, 3 F.3d at 417.

C. Analysis of Expert Testimony

Establishing a sound and reliable medical theory connecting the vaccine to the injury often requires a petitioner to present expert testimony in support of his or her claim. *Lampe v. Sec'y of Health & Hum. Servs.*, 219 F.3d 1357, 1361 (Fed. Cir. 2000). Vaccine Program expert testimony is usually 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 Cedillo v. Sec'y of Health & Hum. Servs.*, 617 F.3d 1328, 1339 (Fed. Cir. 2010) (*citing Terran v. Sec'y of Health & Hum. Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999). "The *Daubert* factors for analyzing the reliability of testimony are: (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community." *Terran*, 195 F.3d at 1316 n.2 (citing *Daubert*, 509 U.S. at 592-95).

The *Daubert* factors play a slightly different role in Vaccine Program cases than they do when applied in other federal judicial fora. *Daubert* factors are employed by judges to exclude evidence that is unreliable and potentially confusing to a jury. In Vaccine Program cases, these factors are used in the weighing of the reliability of scientific evidence. *Davis v. Sec'y of Health & Hum. Servs.*, 94 Fed. Cl. 53, 66-67 (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"). The flexible use of the *Daubert* factors to evaluate persuasiveness and reliability of expert testimony has routinely been upheld. *See*, e.g., *Snyder*, 88 Fed. Cl. at 743. In this matter, (as in numerous other Vaccine Program cases), *Daubert* has not been employed at the threshold, to determine what evidence should be admitted, but instead to determine whether expert testimony offered is reliable and/or persuasive.

Respondent frequently offers one or more experts of his own in order to rebut a petitioner's

case. 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*, 219 F.3d at 1362). 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. 136, 146 (1997)). A "special master is entitled to require some indicia of reliability to support the assertion of the expert witness." *Moberly*, 592 F.3d at 1324. 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. *Id.* 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").

D. Consideration of Medical Literature

Finally, although this decision discusses some but not all of the medical literature in detail, I have reviewed and considered all of the medical records and literature submitted in this matter. *See Moriarty v. Sec'y of Health & Hum. Servs.*, 844 F.3d 1322, 1328 (Fed. Cir. 2016) ("We generally presume that a special master considered the relevant record evidence even though [s]he does not explicitly reference such evidence in h[er] decision."); *Simanski v. Sec'y of Health & Hum. Servs.*, 115 Fed. Cl. 407, 436 (2014) ("[A] Special Master is 'not required to discuss every piece of evidence or testimony in her decision.'" (citation omitted)), *aff'd*, 601 F. App'x 982 (Fed. Cir. 2015).

VI. Analysis

Because Petitioner does not allege an injury listed on the Vaccine Injury Table, his claim is classified as "off-Table." As noted above, to prevail on an "off-Table" claim, Petitioner must prove by preponderant evidence that he suffered an injury and that this injury was caused by the vaccination at issue. *See Capizzano*, 440 F.3d at 1320.

A. Persuasiveness of the Experts

Although both experts are qualified to opine in this case, I found Dr. Whitton to be more persuasive than Dr. Steinman with respect to the causal theories discussed by each expert. In particular, Dr. Whitton's deep knowledge of the chemistry at play in this case rendered his opinion more persuasive than that of Dr. Steinman. Dr Whitton holds a Ph.D. in immunology. He has spent his career studying molecular biology, virology, and immunology. *See generally*, Whitton CV. This expertise is borne out in his comprehensive expert reports, which discuss these issues with precision and clarity. This view of the experts is in accord with the opinion expressed by the Chief Special Master in *Trollinger*, where he noted that Dr. Whitton's expert reports, when discussing biochemistry and immunology, "demonstrated far more precision and care in terminology than Dr. Steinman's efforts." *Trollinger v. Sec'y of Health & Hum. Servs.*, No. 16-473V, 2023 WL 2521912

(Fed. Cl. Spec. Mstr. Feb. 17, 2023), *mot. rev. den'd*, No. 16-473V, 167 Fed. Cl. 127 (2023). Based on my assessment of the credibility of the experts, I have afforded Dr. Whitton's opinion more weight than the opinion of Dr. Steinman.

B. *Althen* Prongs Two and Three

While Dr. Steinman has articulated his position describing that the Prevnar vaccine "did cause" Petitioner's condition and the timeframe that is medically acceptable, I need not reach those questions. My findings, discussed in the next section, that Petitioner's causal theories are not sound and reliable, make analysis of either *Althen* prong two or *Althen* prong three unnecessary. *See, e.g.*, *O.M.V. v. Sec'y of Health & Hum. Servs.*, 157 Fed. Cl. 376, 389 (2021) (*quoting DePena v. Sec'y of Health & Hum. Servs.*, 133 Fed. Cl. 535, 549 (2017) (" '[A] petitioner must satisfy all three prongs of the *Althen* test; a failure to satisfy one prong is fatal to the case.' ").[10]

C. *Althen* Prong One

Under *Althen's* first prong, the causation theory must relate to the alleged injury. Petitioner must provide a "reputable" medical or scientific explanation, demonstrating that the vaccine received can cause the type of injury alleged. *Pafford v. Sec'y of Health & Hum. Servs.*, 451 F.3d 1352, 1355-56 (Fed. Cir. 2006). The theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Hum. Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). It must only be "legally probable, not medically or scientifically certain." *Id.* at 549.

I note at the outset that special masters have arrived at different conclusions regarding the viability of the causal theories proposed in this case. Several different special masters have found for Petitioner. *See, e.g.*, *Cooper v. Sec'y of Health & Hum. Servs.*, No. 18-1885V, 2024 WL 1522331, at *1 (Fed. Cl. Spec. Mstr. Mar. 12, 2024); *Anderson v. Sec'y of Health & Hum. Servs.*, No. 18-484V, 2024 WL 557052 (Fed. Cl. Spec. Mstr. Jan. 17, 2024); *Parker v. Sec'y of Health & Hum. Servs.*, No. 20-411V, 2023 WL 9261248 (Fed. Cl. Spec. Mstr. Dec 20, 2023); *Sprenger v. Sec'y of Health & Hum. Servs.*, No. 18-279V, 2023 WL 8543435 (Fed. Cl. Spec. Mstr. Nov. 14, 2023); *Pierson v. Sec'y of Health & Hum. Servs.*, No. 17-1136V, 2022 WL 322836, at *31 (Fed. Cl. Spec. Mstr. Jan. 19, 2022); *Gross v. Sec'y of Health & Hum. Servs.*, No. 17-1075V, 2022 WL 9669651 (Fed. Cl. Spec. Mstr. Sep. 22, 2022); *Maloney v. Sec'y of Health & Hum. Servs.*, No. 19-1713V, 2022 WL 1074087 (Fed. Cl. Spec. Mstr. Mar 17, 2022); *Koller v. Sec'y of Health & Hum. Servs.*, No.16-439V, 2021 WL 5027947 (Fed. Cl. Spec. Mstr. Oct. 8, 2021). The Chief Special Master has rejected the causal theories proposed in this case and has denied entitlement. *See, e.g.*, *Gamboa-Avila v. Sec'y of Health & Hum. Servs.*, No. 18-925V, 2023 WL 6536207 (Fed. Cl. Spec. Mstr. Sept. 11, 2023), *mot. rev. den'd*, No. 18-925V, 170 Fed.Cl. 441 (2024), *appeal docketed*, No. 2024-1765 (Fed. Cir. May 1, 2024); *Trollinger*, 2023 WL 2521912, at *28, *mot. rev. den'd* 167 Fed.Cl. 127 (2023); *Bielak v. Sec'y of Health & Hum. Servs.*, 18-761V, 2023 WL 35509 (Fed.

[10] While evidence used to support *Althen* prongs two and three can also be considered in an *Althen* prong one analysis, I have considered such evidence and conclude that it does not alter my *Althen* prong one finding. *Capizzano*, 440 F.3d at 1326 (evidence used to satisfy one of the *Althen* prongs can be used to satisfy another *Althen* prong); *but see Althen*, 418 F.3d at 1278 (temporal association alone is insufficient to establish causation).

Cl. Spec. Mstr. Jan. 3, 2023); *Deshler v. Sec'y of Health & Hum. Servs.*, No. 16-1070V, 2020 WL 4593162 (Fed. Cl. Spec. Mstr. July 1, 2020).

1. Phosphoglycerol Theory

Petitioner's first causal theory can be summarized as follows: Phospholipids are components of the myelin sheath. Phosphoglycerol is present in Prevnar 13. Phosphoglycerol induces antibodies that then, via molecular mimicry, target phosphoglycerol on phospholipids in host nerves. This results in GBS. For the reasons discussed below, I find that Petitioner has not presented a sound and reliable causation theory.

a. *Pneumococcal infection is not a known cause of GBS*

Approximately two-thirds of GBS cases have been linked to a preceding infection. Jasti et al., *Guillain-Barré syndrome: causes, immunopathogenic mechanisms and treatment*, 12 EXPERT REVIEW OF CLINICAL IMMUNOLOGY 11, 1175-89, 1176 (2016) (filed as Ex. B, Tab 16) (hereinafter "Jasti"). Dr. Whitton opined that if Dr. Steinman's theory were correct, that the bacterial polysaccharides in Prevnar 13 cause GBS via molecular mimicry, then "it would be reasonable to assume that the organism from which these polysaccharides are taken – *S. pneumoniae* – also would cause GBS." First Whitton Rep. at 8. This principle is frequently referred to in Program cases, often by petitioners, who note that an infection's ability to cause a particular disease lends support for a causal theory involving the vaccine and that same disease. *See e.g.*, *Wilson v. Sec'y of Health & Hum. Servs.*, No. 17-1265V, 2023 WL 9053671, at * 13 (Fed. Cl. Spec. Mstr. Dec 7, 2023) (agreeing with medical literature that in order for a vaccine to cause autoimmunity, the infection should as well). Jasti lists approximately three dozen infections that have been noted to precede GBS. They include: "Mycoplasma pneumoniae, Haemophilus influenzae, Salmonella species, Mycobacterium bovis, Brucella, Orientia tsutsugamushi, Legionella pneumophila, Bartonella henselae, Helicobacter pylori, Francisella tularensis, Borrelia, cytomegalovirus, Epstein–Barr virus, varicella-zoster virus, influenza virus, human immunodeficiency virus, parainfluenza virus type 1, adenovirus, herpes simplex virus, hepatitis (A, B, and E), Japanese encephalitis virus, West Nile virus, enterovirus (D68, 71), Hantavirus, measles, Parvovirus B19, Norovirus, parechovirus, Coxsackieviruses, Echovirus, mumps, rubella, polio (wildtype 3), dengue, chikungunya, and Zika viruses." *Id.* Pneumococcal infection is not a recognized GBS trigger.

This raises the question: why would phosphoglycerol in the Prevnar 13 vaccine cause GBS via molecular mimicry if the phosphoglycerol in *S. pneumoniae* does not?

Dr. Steinman attempted to answer that question, albeit unpersuasively. He stated that the Prevnar 13 vaccine "is very different" than *S. pneumoniae*. Second Steinman Rep. at 9. He noted that the sugars in the vaccine are connected to CRM_{197}, which is not the case in the bacteria. *Id.* He also pointed out that the vaccine contains alum while the bacteria does not. *Id.* In his final point, Dr. Steinman stated that "the linkage between CRM_{197} and the sugars is via the glycerophosphate chemical moiety and this is not the situation in S. pneumoniae where there is no chemical linkage to the protein CRM_{197}." *Id.* However, none of these points 1) addresses the fact that the antigens in the vaccine are immunologically similar to the antigens in the bacterium (indeed, they need to

be in order for the vaccine to be effective); or 2) explains why these differences are at all significant. In fact, Dr. Whitton referred to them as a "smokescreen." Second Whitton Rep. at 4. A molecular mimicry theory specifically relies on immunologic similarities between an antigen and self-tissue. If those same similarities are present in both the vaccine and the bacterium, the fact that the bacterium is not associated with GBS is significant.

The lack of an association between *S. pneumoniae* and GBS likely relates to the structure of the bacterium itself. First Whitton Rep. at 9. Bacterium are surrounded by cell walls, which can be differentiated by the ability of an injected dye to penetrate and remain in these walls. *Id.* Gram positive bacteria have a thick cell wall, while Gram negative bacteria are characterized by a thin cell wall. *Id.* One unique feature of Gram negative bacteria is that these bacteria are surrounded by an outer membrane "in the surface of which are embedded the bacterial LOS/LPS[11] molecules that are thought to be involved in GBS." *Id.* These LOS/LPS molecules are only expressed by certain Gram negative bacteria. *Id. S. pneumoniae* is Gram positive and thus does not express LOS/LPS molecules. *Id.* In fact, all of the bacteria referenced by Jasti as implicated in triggering GBS are Gram negative except one, which Dr. Whitton describes as Gram neutral, "because it has a unique cell wall that is all but impenetrable to routine stains (including Gram)." *Id.* at 9-10. Dr. Whitton opined that "[t]he absence of any standard Gram-positive bacteria from [Jasti]'s exhaustive list is striking and is consistent with the notion that these bacteria do not contain the molecules necessary to trigger GBS. It follows that Prevnar 13, too, lacks those molecules." *Id.* at 10.

Petitioners are not required to demonstrate that a vaccine's infectious counterpart is a known-disease trigger. However, just as this evidence is often persuasive when it exists, its notable absence reduces the persuasiveness of Petitioner's causal theory in the case at bar.

b. *There is not a documented association between PCV-13 and GBS*

Baxter et al. identified cases of hospitalized GBS patients from Kaiser Permanente from 1995 through 2006. They compared "the odds of vaccination in the 6 and 10 weeks prior to onset of GBS to the odds of vaccination during the same time intervals in all vaccinated individuals in the entire KPNC population." Baxter at 197. Baxter et al. studied PPSV23 and not PCV13. They concluded that there was no evidence "of an increased risk of GBS following vaccinations of any kind." *Id.* Tseng et al. conducted a retrospective cohort study examining the risk of adverse events after the PCV13 and PPSV23 vaccines; it included 313,136 doses of the PCV13 vaccine and 232,591 doses of PPSV23. Tseng at 1. Tseng et al. concluded that the incidence rate of adverse events, including GBS, after PCV13 was no more common than after PPSV23. *Id.* at 7. In noting that pneumococcal vaccines do not pose a higher risk of GBS, Dr. Steinman observed that "these epidemiological studies are reassuring" but opined that they do not rule out that the PCV13 vaccine could cause GBS. First Steinman Rep. at 24.

[11] Lipo-oligosaccharides and lipopolysaccharides are molecules expressed by some bacteria – some of which have ganglioside-like structures. First Whitton Rep. at 8. *See, e.g.*, Komagamine & Yuki, who note that "[t]he LOS of *C. jejuni* isolated from a GBS patient had structures identical to the terminal tetrasaccharide of the GM1 expressed on peripheral nerves." Komagamine & Yuki at 393.

Haber et al. assessed reports of adverse events in adults aged 19 years and older who received PCV13 that were reported to the Vaccine Adverse Event Reporting System (VAERS) from June 2012 to December 2015. During this time, approximately 16 million doses of the PCV13 vaccine were administered, and 11 reports of GBS within 42 days of vaccination were filed. First Whitton Rep. at 10; Haber at 6334. This amounts to a rate of 0.7 cases of GBS per million doses of the vaccine, which is lower than the background rate for GBS of approximately 1-2 cases per 100,000. Haber at 6334; First Whitton Rep. at 10.

While these studies are not dispositive on the issue of causation, the lack of an association between pneumococcal vaccination and GBS provides some evidence that the PCV13 vaccine does not cause GBS.

c. *Gangliosides, not phospholipids, are a likely target in GBS*

The pathological role of anti-ganglioside antibodies in GBS is well accepted in the scientific community. Rinaldi & H. Willison, *Ganglioside antibodies and neuropathies*, 21 CURR OPIN NEUROL 540-46 (2008) (filed as Ex. B, Tab 15); H. Willison, *The immunobiology of Guillain-Barré syndromes*, 10 JOURNAL OF THE PERIPHERAL NERVOUS SYSTEM 94-112 (2005) (filed as Ex. B, Tab 7); Y. Komagamine & N. Yuki, *Ganglioside mimicry as a cause of Guillain-Barré syndrome*, 5 CNS & NEUROLOGICAL DISORDERS -- DRUG TARGETS 4, 391-400 (2006) (filed as Ex. B, Tab 13) (hereinafter "Komagamine & Yuki"). P. van Doorn, *Clinical features, pathogenesis, and treatment of Guillain-Barré syndrome*, 7 LANCET NEUROLOGY 939-50 (2008) (filed as Ex. B, Tab 6) Van den Berg et al., *Guillain-Barré syndrome: pathogenesis, diagnosis, treatment and prognosis*, 10 NATURE REVIEWS NEUROLOGY 469-82 (2016) (filed as Ex. B, Tab 12) (hereinafter "Van den Berg").

Dr. Whitton testified that while it is recognized that gangliosides are target molecules in GBS, "giants" in the field of GBS have not mentioned anything about phospholipids causing the disease. Tr. at 317. Petitioner argues that GBS experts do not contend that gangliosides are the *only* target antigen in GBS. Tr. at 364. Dr. Whitton acknowledged this point, but opined that although other target antigens have been discussed in the literature, none of this literature discusses phospholipids or phosphoglycerol. *Id.*

> They write reviews about the pathogenesis of GBS. What causes this disease? They don't mention phospholipids. They don't mention phosphoglycerol. And I recognize that old trope of absence of evidence is not evidence of absence, but if world leaders in the field are describing pathogenesis of GBS and they don't mention phospholipids or phosphoglycerol, well, I'm going to draw a conclusion from there.

Id.

Indeed, in the Kanter paper (Dr. Steinman was a co-author) the authors remarked that, "[l]ipids are important targets of immune responses in a variety of microbial and autoimmune diseases. Autoimmune responses directed against phospholipids and gangliosides contribute to the pathogenesis in systemic lupus erythematosus and Guillain-Barré syndrome, respectively." Kanter

at 138. Kanter states that gangliosides -- and not phospholipids -- contribute to the pathogenesis of GBS. If scientists believed that phospholipids were target antigens in GBS, the authors would not have used the word "respectively." During the entitlement hearing, Dr. Steinman discussed the Kanter article. *See* Tr. at 28-32. He testified that the above sentence is correct, but that gangliosides are not the only target antigen in GBS. *Id.* at 31-32. However, Dr. Steinman did not discuss the plain meaning of the sentence with respect to phospholipids -- that according to Kanter at al., they are not implicated in the pathogenesis of GBS.

Petitioner relies on several pieces of medical literature to support his phosphoglycerol causation theory. Specifically, Petitioner points to Gilburd and Nakos as support for the point that some GBS patients have autoantibodies to phospholipids.

Gilburd et al., *Autoantibodies to Phospholipids and Brain Extract in patients with the Guillain-Barre Syndrome: Cross-Reactive or Pathogenic*?, 16 AUTOIMMUNITY 23 (1993) filed as Ex. 32) (hereinafter "Gilburd"). Gilburd et al. studied the reactivity of GBS sera with various phospholipids. Gilburd at 23. Their results indicated that six out of the 16 GBS sera studied had antibodies to one of more phospholipid antigens. *Id.* Although Gilburd et al. found that some patients with GBS produced autoantibodies to phospholipids, they concluded these autoantibodies were "probably produced as a result of the myelin damage rather than [a] cause [of] the demyelination." *Id.*

Nakos et al. took four blood samples from nine patients with GBS and nine controls before and after GBS treatment. Nakos et al., *Anti-phospholipid antibodies in serum from patients with Guillain-Barré syndrome*, 31 INTENSIVE CARE MED. 1401 (2005) (filed as Ex. 33) (hereinafter "Nakos"). Nakos tested the samples for IgM, IgA, and IgG antibodies to phosphatidylcholine, phosphatidylinositol, cardiolipin, phosphatidic acid, phosphatidylserine, phosphatidylglycerol, phosphatidylethanolamine, sphingomyelin, and gangliosides. Nakos at 1401. The study detected anti-phospholipid antibodies in all the GBS patients and in none of the controls. *Id.* Nakos et al. noted that "[i]t is not well understood whether these anti-phospholipid antibodies play a role in the pathogenesis of the polyneuropathy or represent a part of a more extensive immunoreaction that takes place in the GBS." *Id.* at 1406. Nakos et al. concluded that there was "no relationship between the presence of anti-phospholipid antibodies and outcome, nor to the severity of the disease."[12] *Id.* at 1407. The question that Dr. Whitton posed is salient: "If anti-phospholipid antibodies are pathogenic, why is there no relationship between them, and the severity / outcome of GBS?" Second Whitton Rep. at 7.

Although Gilburd and Nakos do not support the pathogenic role of phospholipids in GBS, Petitioner attempts to establish this connection through the Ho study. Ho et al., *Identification of Naturally Occurring Fatty Acids of the Myelin Sheath That Resolve Neuroinflammation*, 4 SCI. TRANSLATIONAL MED. 137, 1-13 (2012) (filed as Ex. 35) (hereinafter "Ho"). Ho et al. found that autoantibodies against phospholipids contribute to demyelination in multiple sclerosis. However, MS and GBS are different diseases. And while it is true that myelin contains phospholipids,

[12] This is dissimilar to the research on anti-ganglioside antibodies and GBS, which demonstrates that "there is a relation between the presence of [anti-gangiolside] antibodies and the clinical symptoms and severity of GBS." Van den Berg at 941.

Petitioner has not presented any persuasive evidence that GBS is mediated by an attack on phospholipids. "It is simply speculative to propose that GBS could be *mediated by an attack on this target*, based solely on the logic that the myelin *contains* it." *Gamboa-Avila* at *27.

When I consider the evidence in its entirety, I conclude that Petitioner has not presented a sound and reliable theory describing how the phosphogycerol in the Prevnar vaccine can cause GBS.

2. CRM_{197} and Contactin-1 Theory

Dr. Steinman's second molecular mimicry theory involves CRM_{197} and contactin-1. Dr. Steinman identified a homologous sequence between CRM_{197} and contactin-1, W_ _ _ _ALS_E (hereinafter "WEQ sequence"), which he believes would be "capable of inducing a neuroinflammatory disease." First Steinman Rep. at 20.

Contactin-1 is a paranodal protein on the node of Ranvier, a part of a nerve axon where there is no myelin. Tr. at 72-73, 75.

The Prevnar 13 vaccine is a "sterile suspension of saccharides of the capsular antigens of *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 14, 18C, 19A, 19F, and 23F, individually linked to a non-toxic diphtheria CRM_{197} protein." Ex. 30 (hereinafter "Prevnar 13 Vaccine Package Insert) at 24. CRM_{197} is a "nontoxic variant of diphtheria toxin… purified through ultrafiltration, ammonium sulfate precipitation, and ion-exchange chromatography." *Id.* The *s. pneumoniae* serotypes are chemically linked to CRM_{197} in order to induce an immune response. First Whitton Rep. at 6.

In addressing Dr. Steinman's second molecular mimicry theory, I analyze the two molecules involved as I did above for phosphoglycerols and phospholipids. I similarly find that this theory not persuasive.

a. *CRM_{197} is not immunogenic*

Dr. Steinman testified that CRM_{197} was developed to make a "highly immunogenic vaccine" using the diphtheria toxin. Tr. at 72. CRM_{197} differs from the diphtheria toxin by one amino acid. *Id.* Dr. Whitton agreed that CRM_{197} was extremely similar to the diphtheria toxin but disagreed with Dr. Steinman's argument that it was immunogenic. Tr. at 290. Dr. Whitton testified that CRM_{197} was conjugated to trigger a response for children; adults can recognize and respond to "naked, unconjugated polysaccharide bacteria." *Id.*

Dr. Steinman cited to the Raju paper as support for the proposition that CRM_{197} is immunogenic. The Raju paper addresses the diphtheria toxin[13] (DTX) and how it triggers $CD4^+$ T

[13] Toxin: a poison; frequently used to refer specifically to a protein that is produced by some higher plants, certain animals, or pathogenic bacteria and is highly toxic for other living organisms. Such substances are differentiated from the simple chemical poisons and the vegetable alkaloids by their high molecular weight and antigenicity. Toxin, DORLAND'S, https://www.dorlandsonline.com/dorland/definition?id=50415 (last accessed July 16, 2024).

cells. Raju at 3207. I find it notable that in the introduction, the authors distinguish the toxin from the toxoid; "Diphtheria mortality is mainly due to the effects of DTX, the key component of anti-diphtheria vaccines is diphtheria toxoid[14] (DTD), a partially denatured, non-toxic form of DTX." *Id.* This distinguishes the diphtheria toxin from the diphtheria toxoid and CRM_{197}. Dr. Whitton further dispelled the applicability of the Raju paper to Dr. Steinman's molecular mimicry theory by stating the Raju paper does not show a T-cell response to either CRM_{197} or the WEQ sequence. Tr. at 332. The Raju paper technically includes the WEQ sequence but as a part of a longer 20 amino acid sequence, the 151-170 range. Second Whitton Rep. at 13-14. When the authors tested peptide sequences of 20 amino acid lengths, the authors noted six 20 peptide sequences (the 271-290, 321-340, 331-350, 351-370, 411-430 and 431-450 sequences) which were recognized by all subjects. Raju at 3207. This did not include the 151-170 sequence. *Id.*; *see also* Second Whitton Rep. at 13. This is significant because the longer sequence that contains WEQ "is not known to be commonly recognized by the human immune response." *Id.* at 13.

Dr. Whitton additionally noted that the 151-170 sequence generated a very low human immune response when compared with other regions on the diphtheria toxin.

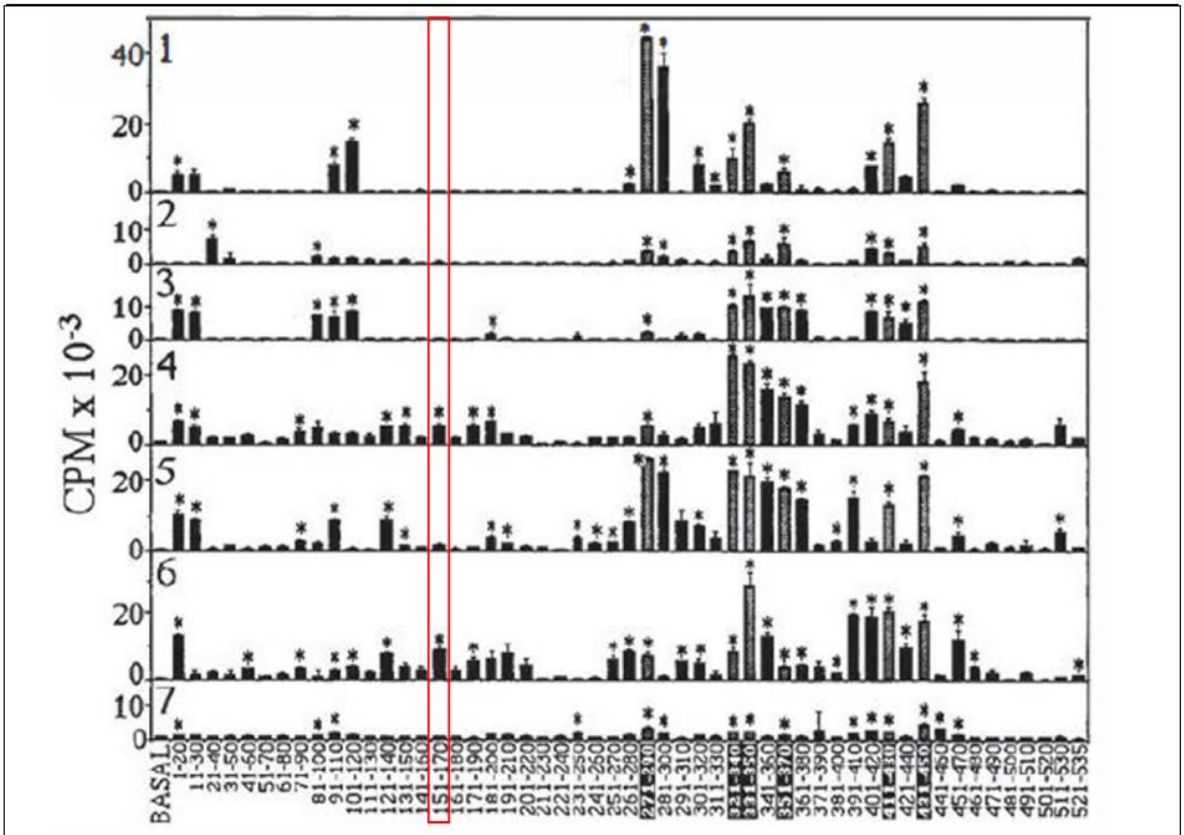


Figure 2. Figure 4 from Raju *et al.* (Exh 66). Red box identifies the T cell responses to the 151-170 peptide of diphtheria toxin

[14] Toxoid: a modified or inactivated bacterial exotoxin that has lost toxicity but retains the properties of combining with, or stimulating the formation of, antitoxin. Toxoid, DORLAND'S, https://www.dorlandsonline.com/dorland/definition?id=50428 (last accessed July 16, 2024).

Second Whitton Rep. at 14. Dr. Whitton contextualized the Raju paper by stating "almost every part of the diphtheria toxin protein appears able to activate human T cells, so the fact that Dr. Steinman's approach allowed him to stumble across a short sequence (WEQAKALSVE) that is part of a stimulatory peptide (151-170) is not at all surprising." *Id.* at 13. To summarize, the Raju paper does not discuss CRM_{197}. The Raju paper also demonstrates that the WEQ sequence (contained with the 151-170 peptide) even in the diphtheria toxin, is not particularly immunogenic. For all these reasons, I find, consistent with the opinion of Dr. Whitton, that the Raju paper does not support Dr. Steinman's argument that CRM_{197} is immunogenic.

As Dr. Whitton has distinguished, CRM_{197} is a protein linked to various streptococcus serotypes for immunization. CRM_{197}, while chemically similar to the diphtheria toxin, is **not** the diphtheria toxin and has no immunogenic qualities. The fact that we still immunize people for diphtheria provides strong support for this point. In other words, CRM_{197} does not confer immunity against diphtheria. Accordingly, I conclude that Petitioner has not presented persuasive evidence that CRM_{197} would cause an autoimmune response.

b. *Contactin-1 as a possible antibody target*

Dr. Steinman opined that contactin-1 is an antibody target in GBS. To support this proposition, Dr. Steinman cited to a number of papers, focusing mostly on the Miura paper. Miura et al., *Contactin 1 IgG4 associates to chronic inflammatory demyelinating polyneuropathy with sensory ataxia*, 138 BRAIN 1484-91 (2015) (filed as Ex. 43) (hereinafter "Miura"). The Miura paper was a case study involving 533 patients with CIDP and use of their blood to find a potential biomarker to guide treatment options for CIDP patients. Miura at 1484. Importantly, blood from 200 GBS patients and 100 MS patients were used as disease *controls*. *Id.* at 1485. The authors found that "[t]hirteen of 533 (2.4%) patients with chronic inflammatory demyelinating polyneuropathy had anti-contactin-1 IgG4 antibodies whereas neither patients from disease or normal control subjects did." Miura at 1484. The authors also found that "The presence of anti-contactin-1 IgG4 antibodies was significantly more frequent in CIDP than GBS, multiple sclerosis and normal controls." *Id.* at 1496. While the crux of the paper is about contactin-1 IgG4 antibodies, as noted by Dr. Steinman, IgG2 antibodies to contactin-1 were identified in five GBS patients and three CIDP patients. First Steinman Rep. at 15; *see also* Miura at 1486. Notably, however, this paper does not discuss GBS in any meaningful capacity. Nor does Dr. Steinman. He dedicates one sentence to the topic in his first expert report. First Steinman Rep. at 24. Although he addresses it further in his second report, Dr. Steinman does not substantively discuss the finding in Miura, that five GBS patients had IgG2 antibodies to contactin-1, beyond noting that contactin-1 antibodies have been observed in GBS. Second Steinman Rep. at 7. As discussed by Dr. Callaghan, these antibodies are of "unclear clinical significance." Second Callaghan Rep. at 2. Dr. Callaghan described Dr. Steinman's suggestion that antibodies to contactin-1 are a known cause of GBS to be "quite misleading." *Id.* While CIDP and GBS are both demyelinating neuropathies, the authors of the Miura paper made it a point to use GBS patients as part of their control group, signaling they do not find contactin-1 antibodies in GBS to be salient. *See, e.g., Moran v. Sec'y of Health & Hum. Servs.*, No. 16-538V, 2021 WL 4853544 at *27 (Fed. Cl. Spec. Mstr. Oct. 4, 2021) (finding a piece of medical literature discussing an association between rheumatoid arthritis and the flu vaccine unpersuasive when the authors used the flu vaccine as a control).

Dr. Steinman also cited to Fehmi and Manso papers to address how contactin-1 may be connected to GBS. Fehmi et al., *Nodes, paranodes and neuropathies*, 89 J NEUROL NEUROSURG PSYCHIATRY, 61-71 (2018) (filed as Ex. 41) (hereinafter "Fehmi"); Manso et al., *Contactin-1 IgG4 antibodies cause paranode dismantling and conduction defects*, 139 BRAIN 1700-12 (2016) (filed as Ex. 42) (hereinafter "Manso"). In the Fehmi paper, in discussion of neuropathies, the authors note that "nodal adhesion molecules, in particular [neurofascin]155 (NF), NF186, GLDN, and contactin are targeted in some neuropathies traditionally considered 'demyelinating,' such as CIDP." Fehmi at 66. The authors separately note that "Antiganglioside antibodies were the first serum antibodies to be linked with GBS. There is a particularly strong association with Miller Fisher syndrome (MFS) subtype, in which antibodies against the GQ1b ganglioside are detected in 95%-99% of cases." *Id.* at 63. The Manso paper, similar to the Miura paper, is a study of contactin-1 and CIDP in rats, which did find some paranodal destruction. Manso at 1700. All three papers suggest a link between contactin-1 and CIDP, but **not** GBS. I find it notable that the Miura paper used GBS patients as a control, which shows that the authors of the paper and the broader scientific community believe these two diseases processes are indeed separate and distinguishable from one another. As noted in the Fehmi paper, researchers still correlate GBS with anti-ganglioside antibodies. These papers do not provide sound and reliable evidence in support of Petitioner's burden.

c. *Molecular mimicry between contactin-1 and CRM_{197}*

Dr. Whitton opined during the entitlement hearing that the WEQ sequence from the vaccine had amino acid similarities with contactin-1 due to chance and not because it is a significant enough length to generate an immunogenic reaction. Tr. at 330-31. Dr. Whitton elaborated in his expert reports that the e-value[15] associated with Dr. Steinman's BLAST searches are high, demonstrating they are products of chance rather than truly significant homology. Specifically, Dr. Whitton stated that an e-value must be less than $3.9x10^{-7}$, and Dr. Steinman's results are "millions of times higher than required." First Whitton Rep. at 22. Dr. Steinman contested this view, opining that the Gautam and Root-Bernstein[16] papers substantiate his BLAST search results with 5 of 10 amino acid matches.

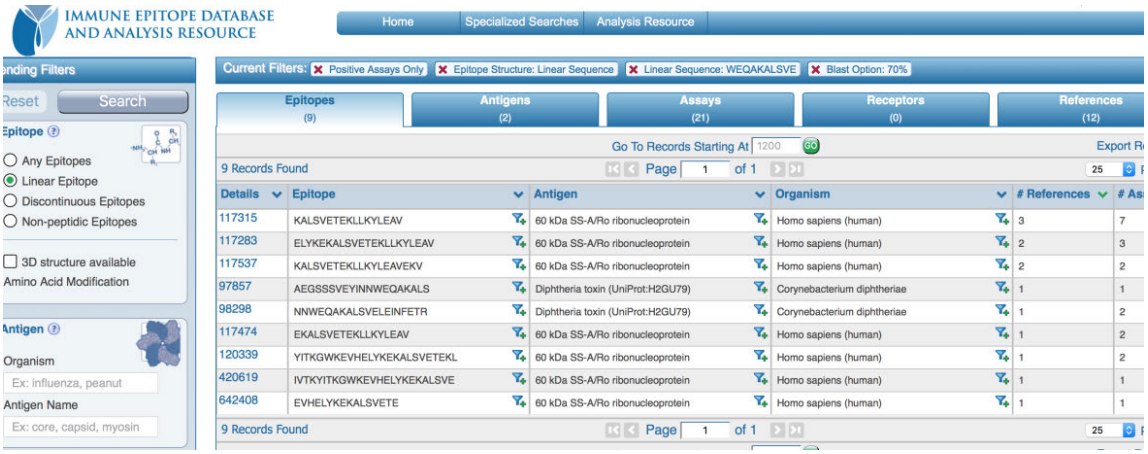
The Gautam papers, which were co-authored by Dr. Steinman, have been cited in cases where Dr. Steinman proposes molecular mimicry as a causal mechanism. Exs. 44-46. I do not find these papers, standing alone, to be persuasive in demonstrating that 5 of 10 amino acids is sufficient

[15] "The Expect value (E) is a parameter that describes the number of hits one can "expect" to see by chance when searching a database of a particular size. It decreases exponentially as the Score (S) of the match increases." First Whitton Rep. at 20.

[16] Dr. Steinman additionally cited to the Root-Bernstein paper to support his contention that 5 of 10 amino acids constitutes sufficient homology. Second Steinman Rep. at 19. Dr. Whitton criticized the Root-Bernstein paper because the author misunderstood the concept of E-values. Second Whitton Rep. at 11. In his third report, Dr. Steinman conceded that Root-Bernstein's comments about E-Value was "backwards" and "hard to understand." Third Steinman Rep. at 23. During the entitlement hearing, Dr. Steinman admitted there were "problems with the methodology used in the Root-Bernstein paper." Tr. at 384-85.

homology to trigger neuroinflammation. Other special masters share this view. *See, e.g.*, *L.R. v. Sec'y of Health & Hum. Servs.*, No. 16-922V, 2024 WL 1912575 at *19 (Fed. Cl. Spec. Mstr. Mar. 28, 2024); *Sparrow v. Sec'y of Health & Hum. Servs.*, No. 18-295V, 2024 WL 1599165 at *25-27 (Fed. Cl. Spec. Mstr. Mar. 19, 2024), mot. rev. docketed (Apr. 18, 2024); *Trollinger*, 2023 WL 2521912, at *29; *Schilling v. Sec'y of Health & Hum. Servs.*, No. 16-527V, 2022 WL 1101597, at *5, 19–20 (Fed. Cl. Spec. Mstr. Mar. 17, 2022); *McKown*, 2019 WL 4072113, at *50.

Dr. Steinman used an additional step to buttress his theory. He ran the WEQ sequence through the Immune Epitope Database (IEDB) to demonstrate that the sequence has been studied and has been found in various immune cell assays. Second Steinman Rep. at 17-19. Drs. Steinman and Whitton disagree on how helpful the IEDB search results are. Dr. Whitton points out that the IEDB "filter" results contain the WEQ sequence but the WEQ sequence is embedded in much longer sequences, therefore Dr. Steinman's proposed 5 of 10 or 5 of 12 homologies criteria is lost in the IEDB results. First Whitton Rep. at 24-25. Reproduced below is Dr. Steinman's IEDB filtration results, which show sequences of at least 15 amino acids (First Steinman Rep. at 21).



Based on this, it is unclear whether the WEQ sequence is significant, even within the parameters of Dr. Steinman's theory. As Dr. Whitton stated, "how do we know what part of that longer peptide is recognized by the immune response?" Second Whitton Rep. at 12. Dr. Whitton noted that none of the IEDB results for the WEQ sequence found contactin-1 as a homologous epitope. The results broadly identify that the WEQ sequence is found in humans, or homo sapiens, but 0 results are found for human contactin-1. Second Whitton Rep. at 14.

Dr. Steinman cited to the Raju paper as a "further validation" of his three-step filtration method. Second Steinman Rep. at 20-24. As discussed previously, I find the Raju paper unpersuasive regarding to the immunogenicity of CRM_{197}. Furthermore, the IEDB results did not turn up any information on contactin-1, or "the other side of the coin", as Dr. Whitton described it. Second Whitton Rep. at 14. Based on the above, I find that Petitioner has not presented a preponderance of evidence in support of molecular mimicry between CRM_{197} and contactin-1, and further, how this mimicry could cause GBS.

I do not find either Dr. Steinman's phosphoglycerol theory or his CRM_{197}-contactin-1 theory to be sound and reliable. Accordingly, I conclude that Petitioner has not presented

preponderant evidence with respect to *Althen* prong one. The failure to meet *Althen* prong one is fatal to Petitioner's claim.

VII. CONCLUSION

Upon careful evaluation of all the evidence submitted in this matter, including the medical records, medical literature, as well as the experts' opinions and testimony, I conclude that Petitioner has not provided preponderant evidence with respect to the first *Althen* prong. His petition is accordingly dismissed.

In the absence of a motion for review filed pursuant to RCFC Appendix B, the Clerk of Court **SHALL ENTER JUDGMENT** in accordance with this decision.[17]

IT IS SO ORDERED.

s/ Katherine E. Oler
Katherine E. Oler
Special Master

[17] Pursuant to Vaccine Rule 11(a), the parties may expedite entry of judgment by filing a joint notice renouncing their right to seek review.