In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 17-69V

J.C.,

Petitioner,

v.

SECRETARY OF HEALTH AND HUMAN SERVICES,

Respondent.

Filed: May 16, 2024
Refiled as Redacted: July 15, 2024

Danielle Anne Strait, Magio Christopher & Toale, PA, Seattle, WA, for petitioner
Ryan Daniel Pyles, U.S. Department of Justice, Washington, DC, for respondent

Decision[1]

On January 17, 2017, petitioner, J.C., filed a petition under the National Childhood Vaccine Injury Act, 42 U.S.C. § 300aa-10-34 (2018)[2], alleging that her influenza ("flu") vaccination she received on February 3, 2014, and her human papillomavirus ("HPV") vaccination she received on February 20, 2014, caused her to develop narcolepsy/cataplexy. (ECF No. 1, p. 1; ECF No. 75, p. 1.) For the reasons set forth below, I conclude that petitioner is *not* entitled to an award of compensation.

I. Applicable Statutory Scheme

Under the National Vaccine Injury Compensation Program, compensation awards are made to individuals who have suffered injuries after receiving vaccines. In general, to gain an award, a petitioner must make a number of factual demonstrations, including showing that an individual received a vaccination covered by the statute;

[1] When this decision was originally filed the undersigned advised his intent to post it 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). In accordance with Vaccine Rule 18(b), petitioner filed a timely motion to redact certain information. This decision is being reissued with petitioner's name reduced to initials. Except for those changes and this footnote, no other substantive changes have been made. This decision will be posted on the court's website with no further opportunity to move for redaction.

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

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

In many cases, however, the vaccine recipient may have suffered an injury *not* of the type covered in the Vaccine Injury Table. In such instances, an alternative means exists to demonstrate entitlement to a Program award. That is, the petitioner may gain an award by showing that the recipient's injury was "caused-in-fact" by the vaccination in question. § 300aa-13(a)(1)(B); § 300aa-11(c)(1)(C)(ii). In such a situation, of course, the presumptions available under the Vaccine Injury Table are inoperative. The burden is on the petitioner to introduce evidence demonstrating that the vaccination actually caused the injury in question. *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005); *Hines v. Sec'y of Health & Human Servs.*, 940 F.2d 1518, 1525 (Fed. Cir. 1991). In this case, petitioner has alleged that the flu vaccine or the HPV vaccine caused her to suffer narcolepsy with cataplexy, which is not listed on the Vaccine Injury Table relative to the flu vaccine or the HPV vaccine. Petitioner must therefore meet the burden of proof for establishing causation-in-fact.

The showing of "causation-in-fact" must satisfy the "preponderance of the evidence" standard, the same standard ordinarily used in tort litigation. § 300aa-13(a)(1)(A); *see also Althen*, 418 F.3d at 1279; *Hines*, 940 F.2d at 1525. Under that standard, the petitioner must show that it is "more probable than not" that the vaccination was the cause of the injury. *Althen*, 418 F.3d at 1279. The petitioner need not show that the vaccination was the sole cause but must demonstrate that the vaccination was at least a "substantial factor" in causing the condition, and was a "but for" cause. *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999). Thus, the petitioner must supply "proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury[,]" with the logical sequence being supported by "reputable medical or scientific explanation, *i.e.*, evidence in the form of scientific studies or expert medical testimony." *Althen*, 418 F.3d at 1278; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). A petitioner may not receive a Vaccine Program award based solely on his or her assertions; rather, the petition must be supported by either medical records or by the opinion of a competent physician. § 300aa-13(a)(1).

In what has become the predominant framing of this burden of proof, the *Althen* court described the "causation-in-fact" standard, as follows:

> Concisely stated, Althen's burden is to show by preponderant evidence that the vaccination brought about 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 proximate temporal relationship between vaccination and injury. If Althen satisfies this burden, she is "entitled to recover unless the [government] shows, also by a preponderance of the evidence, that the injury was in fact caused by factors unrelated to the vaccine."

Althen, 418 F.3d at 1278 (citations omitted). The *Althen* court noted that a petitioner need not necessarily supply evidence from medical literature supporting petitioner's causation contention, so long as the petitioner supplies the medical opinion of an expert. *Id*. at 1279-80. The court also indicated that, in finding causation, a Program fact-finder may rely upon "circumstantial evidence," which the court found to be consistent with the "system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants." *Id*. at 1280.

II. Procedural History

This case was originally assigned to Special Master Millman. (ECF No. 4.) Between the time the petition was initially filed and March of 2018, petitioner filed medical records marked as Exhibits 1-8. (ECF Nos. 7-8, 21.) Petitioner filed an expert report by neuroimmunologist Lawrence Steinman, M.D., and accompanying medical literature on March 27, 2018. (ECF Nos. 22-26; Exs. 9-39.) In response, respondent filed responsive reports by neurologist Maryann Deak, M.D., and immunologist Neil Romberg, M.D., in July of 2018. (ECF Nos. 28-30; Exs. A-X.) A second exchange of expert reports then occurred in the autumn of 2018. (ECF Nos. 31-33; Exs. 40-46, Y-CC.)

The case was then reassigned to the undersigned in June of 2019 following Special Master Millman's retirement. (ECF Nos. 38-39.) Shortly thereafter, petitioner filed a third report by Dr. Steinman. (ECF No. 40; Exs. 48-52.) Respondent filed responsive reports by Drs. Deak and Romberg in September of 2019. (ECF Nos. 42-43; Exs. DD-KK.) Petitioner then filed a fourth report by Dr. Steinman and additional medical records. (ECF Nos. 46, 50, 55-56; Exs. 53-56.) In October of 2020, an entitlement hearing was set. (ECF No. 54.) However, petitioner subsequently advised that Dr. Steinman had become unavailable for the hearing as scheduled. (ECF No. 57.) The parties agreed to instead proceed with a fact hearing followed by written submissions pursuant to Vaccine Rule 8(d). (ECF Nos. 58-59.)

In March and April of 2022, petitioner filed additional medical records and a declaration. (ECF Nos. 61, 65; Exs. 57-58.) A fact hearing was held on April 26, 2022. (ECF No. 67 (Transcript of proceedings, hereinafter "Tr.").) Petitioner was the only witness. Thereafter, petitioner filed a final report by Dr. Steinman. (ECF No. 69; Exs.

60-62.) Petitioner filed a motion for a ruling on the written record in October of 2022. (ECF No. 75.) Respondent filed his response in January of 2023. (ECF No. 79.) Petitioner filed her reply and an additional declaration in March of 2023. (ECF Nos. 82-83; Exs. 63-64.)

This matter is now ripe for resolution. I have concluded that the parties have had a full and fair opportunity to develop the record and that it is appropriate to resolve this case without an entitlement hearing. *See Kreizenbeck ex rel. C.J.K. v. Sec'y of Health & Human Servs*., 945 F.3d 1362, 1366 (Fed. Cir. 2020) (citing *Simanski v. Sec'y of Health & Human Servs*., 671 F.3d 1368, 1385 (Fed. Cir. 2012)); *see also* Vaccine Rule 8(d); Vaccine Rule 3(b)(2).

III. Factual History

a. Medical Records

Before she received the vaccines at issue in this case, petitioner had a prior history of HPV infection. (Ex. 1, pp. 294, 1809.) Additionally, on May 3, 2013, petitioner saw Thin Han, M.D., for insomnia. (*Id.* at 561-69.) She explained that she was stressed and finding it hard to fall asleep at night. (*Id.* at 562.) On November 19, 2013, petitioner saw her physician for an ear infection. (*Id.* at 610-17.) She did not mention her insomnia during this visit. (*Id.*) Petitioner had an appointment with Jay Seligman, D.O., on January 3, 2014, during which she also did not mention her insomnia.[3] (*Id.* at 641-48.)

On February 3, 2014, petitioner received a FluMist immunization. (Ex. 1, pp. 649-51; Ex. 7, pp. 42-44.) On February 20, 2014, petitioner saw her physician for neck pain, back problems, and shoulder pain. (Ex. 1, p. 653-60.) During this appointment, petitioner received the third dose of her HPV vaccine. (*Id.* at 655; Ex. 64.)

Petitioner returned to Dr. Han on May 14, 2014, for fatigue and insomnia. (Ex. 1, pp. 667-80.) Dr. Han recommended that petitioner see a respiratory therapist for her fatigue and prescribed trazodone for her insomnia. (*Id.* at 668-69; Ex. 7, pp. 45-47.) Petitioner's diagnoses at this visit included obesity, fatigue, and insomnia. (Ex. 1, pp. 668-69.) Two days later, on May 16, 2014, petitioner emailed Dr. Han and reported that she was having chest pain. (*Id.* at 685-89.) On May 19, 2014, petitioner saw Jeffrey Tan, M.D., regarding her fatigue and reported that she was having "intermittent palpitations and feeling lightheaded." (*Id.* at 690.) She reported that these palpitations started after she took trazodone for insomnia, so she stopped taking the medicine. (*Id.* at 691.) Petitioner's blood test showed a high red blood cell count. (*Id.* at 692.) Additionally, petitioner underwent an EKG, which showed no abnormalities. (*Id.* at 692, 695-96.) Dr. Tan referred petitioner to cardiology for a stress test and recommended avoiding stimulants/caffeine and trazodone. (*Id.* at 693.)

[3] Petitioner submitted additional records from before her vaccination. I thoroughly reviewed these records; however, petitioner's prior medical history is not significant to the analysis that follows apart from what has been summarized.

Petitioner began attending a class for weight control on May 21, 2014. (Ex. 1, pp. 707-10.) Petitioner returned to see Dr. Han to discuss her lab results on May 23, 2014. (*Id.* at 718-25.) Dr. Han reported that all of petitioner's labs were normal. (*Id.* at 719.) Petitioner reported that she began to experience sudden jerking movement and on and off muscle weakness in her legs about three weeks before, along with her fatigue. (*Id.*) Dr. Han referred petitioner to a sleep study. (*Id.*) Petitioner underwent a stress test that came back as normal. (*Id.* at 727.)

On June 5, 2014, petitioner saw neurologist Hong Sik Shin, M.D. (Ex. 1, pp. 754-62.) Petitioner's chief complaint was recorded as "involuntary movement." (*Id.* at 754.) Dr. Shin reported that petitioner had a history of nephrolithiasis and obesity and described "losing posture on laughing and excitement lasting [two] seconds, intermittent shock like [p]ain." (*Id.*) She explained that she experienced sleeping attacks and sleep paralysis. (*Id.*) Dr. Shin assessed petitioner and diagnosed her with narcolepsy with cataplexy. (*Id.* at 756.) Dr. Shin prescribed Vivactil to treat petitioner's cataplexy and Methylin for her narcolepsy. (*Id.*) Dr. Shin ordered a CT scan. (*Id.* at 757-59.) Petitioner underwent this scan on June 12, 2014, which revealed "[n]o acute or gross structural intracranial abnormality." (*Id.* at 759.) Petitioner emailed Dr. Shin on June 10, 2014, and reported that the Vivactil was working well, but requested an increase in Methylin because she was still feeling tired during the day. (*Id.* at 766-69.) Petitioner attended her low calorie diet class on June 11, 2014. (*Id.* at 771-74.)

Petitioner underwent a sleep study beginning on June 14, 2014. (Ex. 1, p. 776-92.) The report from this sleep study found that petitioner's apneas/hypopneas are within normal limits. (*Id.* at 786.) Petitioner's "latency to sleep onset was [three] minutes (normally at 10 to 20 min[utes]). Latency to REM onset was 255 minutes (normally at 90 min[utes]). Sleep efficiency (total sleep time / total time in bed was 90% (normally over 90%)." (*Id.*) Additionally, petitioner's electromyogram and electroencephalogram were normal. (*Id.*) The report suggested some therapeutic measures including weight loss, positional tricks, use of oral appliances, or surgical techniques. (*Id.*) On June 24, 2014, petitioner requested an increase in her Methylin. (*Id.* at 799-803.)

Petitioner had a routine follow up with Dr. Shin for REM narcolepsy on July 7, 2014. (Ex. 1, pp. 826-31.) Dr. Shin reported that petitioner had responded well to Methylin. (*Id.* at 826.) Additionally, Dr. Shin reported that petitioner's cataplexy had responded well to protriptyline. (*Id.*) He explained that petitioner's sleep study had showed delayed REM and poor sleep. (*Id.*) Dr. Shin increased petitioner's protriptyline. (*Id.*) Petitioner went to her low calorie diet class on July 9, 2014. (*Id.* at 832-35.)

On July 31, 2014, petitioner emailed Dr. Shin asking for a referral to Stanford Sleep Disorder Clinic. (Ex. 1, p. 839-42.) Dr. Shin changed petitioner's prescription for her cataplexy to imipramine. (*Id.* at 858-61.) On that same day, petitioner also saw Dr. Logan Schneider, a sleep disorder specialist. (Ex. 4, p. 8.) In the history of present illness, Dr. Schneider reported that petitioner began to notice "herself getting weak

when interacting with strangers," specifically when she was anxious. (*Id.*) Petitioner explained that she began having trouble staying awake while driving to work and began needing naps throughout the day. (*Id.*) Petitioner explained that, by the next month, "she was so weak with excitement that she couldn't even get through one exciting story at work, finding that she was slurring her words, trying to catch her breath, and having face weakness with muscle twitching." (*Id.*) Petitioner saw a neurologist and was diagnosed with narcolepsy and cataplexy and was prescribed protriptyline and Ritalin. (*Id.*) Petitioner stopped taking protriptyline due to side effects and her cataplexy symptoms began to rebound. (*Id.*) Additionally, petitioner began waking up 15 to 20 times throughout the night and having far more vivid dreams. (*Id.* at 8-9.) Petitioner also noted changes in her eating habits, which resulted in weight gain. (*Id.* at 9.) Dr. Schneider noted that petitioner received the nasal flu vaccine two months before her symptoms began. (*Id.*) Dr. Schneider recorded petitioner's narcolepsy symptoms and noted that petitioner suffered from cataplexy in her face, neck, legs, and body muscles; hallucinations, specifically auditory hallucinations; and sleepiness. (*Id.*) Based on these symptoms, Dr. Schneider confirmed petitioner's diagnosis of narcolepsy and started her on Xyrem for sleepiness, Effexor for cataplexy, and continued petitioner's Ritalin. (*Id.* at 11-12.)

Petitioner filed substantial additional medical records subsequent to her evaluation at the Sleep Disorder Clinic. These records show ongoing management of her condition. However, because respondent does not dispute that petitioner was appropriately diagnosed with narcolepsy with cataplexy, it is not necessary to detail this further history. (Ex. A, p. 3.) Based on my review of the records, although petitioner continued to report to her physicians that her narcolepsy began post-vaccination (*e.g.* Ex. 2, p. 2; *see also* Ex. 7, pp. 35-36 (confirmation of VAERS report by petitioner)), the treating physicians generally did not discuss the initial cause of petitioner's condition. In her motion, petitioner cites a single instance wherein Dr. Htoo, petitioner's pulmonologist, indicated in April of 2015 that her narcolepsy was "likely triggered" by her FluMist vaccine.[4] (ECF No. 75-1, p. 26 (citing Ex. 1, p. 1184).) However, Dr. Htoo's basis for this opinion is not indicated in the record.

b. Testimony

A fact finding hearing was held on April 26, 2022 during which petitioner testified. (*See* ECF No. 67, Transcript of Proceedings ("Tr."), filed May 10, 2022.) Petitioner explained that before the events that led to this case, she worked at her family business as a controller and was in charge of the financial decision making for the business. (*Id.* at 7-8.) Additionally, she was in school and studying accounting. (*Id.* at 8.) She was a single mother to one daughter at the time. (*Id.* at 9.) She testified that she was not on any medication, however, she did see her doctor for insomnia at the end of 2013, although, these issues resolved when she moved out of her parents' house. (*Id.* at 11.)

[4] Providing a link to the Kaiser Permanente website, petitioner represents that Dr. Htoo is also board certified in sleep medicine. (ECF No. 75-1, n. 5.) However, as of the last visit to that website on May 3, 2024, Dr. Htoo's board certifications are listed as unavailable. Nonetheless, for purposes of this decision I will assume that Dr. Htoo is board certified in sleep medicine.

Petitioner testified that she scheduled a checkup for her daughter, and, at that visit, both her and her daughter were vaccinated using the FluMist. (Tr. 12.) Petitioner explained that she rarely received the flu vaccine before, however, felt that the mist would be less "harsh on [her] body." (*Id.* at 13.) After she received the vaccine, she testified that she "developed a pain in [her] neck and shoulder," that "radiate[d] from [her] shoulder and [shot] up towards [her] neck." (*Id.*) Petitioner made an appointment in early 2014 for her pain and received an HPV vaccine during this appointment. (*Id.* at 13-14.)

In March of 2014, petitioner drove about two and a half hours to a house her parents were planning on purchasing. (Tr. 14-15.) About 30 minutes into the drive, petitioner became exhausted. (*Id.* at 15.) Petitioner's brother-in-law had to drive her home later that evening because petitioner was afraid to drive. (*Id.*) Petitioner's fatigue continued to affect her when she was driving. (*Id.* at 16.) Soon she also began to experience cataplexy, during which her legs and arms would give out and her face would "screw up a little." (*Id.* at 17.) Because of this, petitioner found it hard to work. (*Id.* at 17-18.) She ended up moving back in with her parents because she did not trust herself to stay awake to watch her daughter. (*Id.* 18.) She depended a lot on her family to help her care for her daughter. (*Id.* at 18-19.)

On Mothers' Day 2014, petitioner broke down and her family encouraged her to see a doctor for her symptoms. (Tr. 19.) She scheduled an appointment at an urgent care who encouraged her to see Dr. Han. (*Id.* at 20.) She was referred to a neurologist and underwent a CT scan. (*Id.*) In June of 2014, petitioner was diagnosed with narcolepsy and cataplexy. (*Id.* at 21.) Petitioner sought a second opinion, and this diagnosis was confirmed. (*Id.*) Petitioner participated in in a sleep study and was prescribed Protriptyline and Ritalin. (*Id.* at 22.) Even while taking these medications, petitioner had to take two naps a day. (*Id.*) Neither of these medications would treat her cataplexy, but she hoped they would help her control her emotions so she would have less episodes. (*Id.*) Her symptoms continued daily. (*Id.* at 22-23.)

Petitioner described that after her diagnosis she stopped hanging out with her friends and had to ensure she would have a place to nap if she went anywhere. (Tr. 23.) She went from being an extremely independent person to having to depend on her family every day. (*Id.*) Additionally, her medication had side effects including mood swings and dry mouth. (*Id.*) Petitioner was unable to take her CPA exams and continue her goal of becoming an accountant. (*Id.* at 23-24.) She had to go off her medications when she became pregnant with her son in May of 2015. (*Id.* at 24-25.) Her symptoms rebounded and she became worried about hurting her baby by falling. (*Id.* at 25.) She also had to rely on her family members to help her take care of her daughter. (*Id.* at 26.) Her symptoms did get better when she was able to restart her medication. (*Id.*) However, she was still unable to drive for longer than ten minutes. (*Id.* at 26-27.)

Petitioner testified to how her diagnosis affected her mental health. (Tr. 27.) She explained that she suffered from depression and that she felt like her life had been taken away from her. (*Id.*) She had to quit her job and relies on her family to help take care of her kids, and she can no longer travel like she used to. (Tr. 28-30.)

IV. Expert Opinions and Qualifications

a. Petitioner's expert, Lawrence Steinman, M.D.[5]

Petitioner's expert, Dr, Lawrence Steinman, filed four reports in this case. (Exs. 9, 40, 48, 53.) His opinion centers around his assertion that petitioner's flu or HPV vaccine could have caused petitioner's narcolepsy via molecular mimicry, and, specifically, that either the flu or HPV vaccine contain mimics for hypocretin-2 or the hypocretin-2 receptor. (*See* Ex. 9, pp. 6-28; Ex. 40, p. 6.) Dr. Steinman explained that molecular mimicry is a theory in which "shared structures on a virus or bacteria or in a vaccine can trigger a cross-reactive response to self." (Ex. 9, p. 7 (citing Lawrence Steinman, *Autoimmune Disease,* SCI. AM. 107, 109 (1993) (Ex. 20, p. 5)).) Dr. Steinman's theory is that these mimics then bind to either lymphocytes, which then bind to the hypocretin-2 receptor, or simply bind to the hypocretin-2 receptor alone, causing the patient to develop narcolepsy. (*Id.*; Ex. 40, pp. 1, 3-6.)

Dr. Steinman explained that decreased levels of hypocretin and abnormalities, generally, in the hypocretin-2 receptor are signs of narcolepsy. (Ex. 9, p. 7 (citing Seiji Nishino et al., *Hypocretin (Orexin) Deficiency in Human Narcolepsy,* 355 LANCET 39 (2000) (Ex. 21); Ling Lin et al., *The Sleep Disorder Canine Narcolepsy is Caused by a Mutation in the* Hypocretin (Orexin) Receptor 2 *Gene,* 98 CELL 365 (1999) (Ex. 22)).) However, he acknowledged that it "remains unproven whether immunity to hypocretin has been reported in narcolepsy." (*Id.* at 8.) Dr. Steinman cited four studies that he claimed "reported immune responses to hypocretin receptor 2 in narcolepsy." (*Id.*) The first study found that patients with narcolepsy thought to be induced by the Pandemrix flu vaccine had antibodies that mimicked peptides on the hypocretin-2 receptor. (*Id.* (citing Syed Sohil Ahmed, *Antibodies to Influenza Nucleoprotein Cross-React with Human Hypocretin Receptor 2,* 7 SCI. TRANSLATIONAL MED. 1 (2015) (Ex. 25)).) According to Dr. Steinman, this mimic binds "precisely at the site where hypocretin binds the receptor." (*Id.* (citing Jie Yin et al., *Structure and Ligand-Binding Mechanism of the Human OX_1 and OX_2 Orexin Receptors,* 23 NATURE STRUCTURAL & MOLECULAR BIOLOGY 293 (2016) (Ex. 26)).) He explained that both a group of scientists in Japan

[5] Dr. Lawrence Steinman received his undergraduate degree at Dartmouth College and his medical degree from Harvard University Medical School. (Ex. 41, p. 1.) He completed a residency in pediatric and adult neurology at Stanford University Hospital. (*Id.*) He is a board certified neurologist and has seen both adult and pediatric patients for nearly 40 years. (Ex. 9, p. 3.) Dr. Steinman currently works as a professor at Stanford University in the Department of Neurology, Pediatrics and Genetics. (*Id.* at 1; Ex. 41, p. 1.) In this role, he has cared for patients with an array of autoimmune disease including "ADEM, Bechet's disease, inflammatory neuropathy, transverse myelitis, neuromyelitis optica (NMO) and multiple sclerosis (MS)." (Ex. 9, p. 1.) He has published over 500 peer reviewed articles. (Ex. 41, pp. 5-47.) Dr. Steinman explained that he has written ten papers on narcolepsy. (Ex. 9, p. 1-3.)

and Oxford found that narcolepsy patients have antibodies to the hypocretin-2 receptor. (*Id.* (citing Susumu Tanaka et al., *Detection of Autoantibodies Against Hypocretin, hcrtr1, and hcrtr2 in Narcolepsy: Anti-Hcrt System Antibody in Narcolepsy,* 29 SLEEP 633 (2006) (Ex. 27); Maria Pia Giannoccaro et al., *Antibodies Against Hypocretin Receptor 2 are Rare in Narcolepsy,* 40 SLEEP 1 (2017) (Ex. 28)).) Finally, Dr. Steinman cited a study that found "some evidence of antibodies to [the hypocretin-2 receptor] in narcolepsy," in some, but not all cases following Pandemrix flu vaccination. (*Id.* (citing Guo Luo et al., *Absence of Anti-Hypocretin Receptor 2 Autoantibodies in Post Pandemrix Narcolepsy Cases,* 12 PUB. LIBR. SCI. (2017) (Ex. 29)).)

Dr. Steinman sought to identify a molecular mimic between HPV vaccines and the hypocretin pathway. Dr. Steinman explained that it is unclear from petitioner's medical records whether she received the Gardasil or Cervarix HPV vaccine. (Ex. 9, p. 6.) However, he explained that both of these vaccines "contain the L1 capsid protein of HPV16 and HPV18." (*Id.* at 6-7 (citing *Gardasil Prescribing Information* [hereinafter Gardasil Package Insert], Ex. 18; *Cervarix Prescribing Information* [hereinafter Cervarix Package Insert], Ex. 19).) Therefore, Dr. Steinman limited his analysis to HPV16 and HPV18. (*Id.* at 7.) He explained that "either or both of the 2013-2014 and 2014-2015 have sequences that cross-react with the nucleoprotein of HCRT-RT." (*Id.*) Specifically, Dr. Steinman described how he "ran [BLAST] searches through the protein data bases of the National Library of Medicine looking for homologies between the HPV16 and HPV18 L1 components," which are common to both vaccines, "to see if there were any homologies with various components of the hypocretin pathway, including hypocretin itself and the [hypocretin-2 receptor]." (*Id.* at 8.) Additionally, Dr. Steinman explained that he also ran BLAST searches for HPV6 and HPV11, which are only found in the Gardasil vaccine. (*Id.*) Dr. Steinman defines a "meaningful molecular mimic" as "a run of [five] or more of 12 amino acids that are identical." (*Id.* (citing Anand M. Gautam et al., *Minimum Structural Requirements for Peptide Presentation by Major Histocompatibility Complex Class II Molecules: Implications in Induction of Autoimmunity,* 91 PROC. NAT'L ACAD. SCI. 767 (1994) (Ex. 31); Anand M. 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 (1998) (Ex. 32)).)

Dr. Steinman's first BLAST of hypocretin versus HPV11 1L protein, which is only found in the Gardasil vaccine, found a sequence of five amino acids that are identical, with three amino acids in a row, which he found to be a sufficient degree of homology "to induce clinical relevant neuroinflammation." (Ex. 9, pp. 11-12.) He found a similar homology between HPV6, which again is found only in the Gardasil vaccine, and hypocretin. (*Id.* at 12-14.) Dr. Steinman then "blasted" HPV18, found in both the Gardasil and Cervarix vaccines, and the hypocretin-2 receptor. (*Id.* at15-16.) He found a sequence that had seven out of 11 identical amino acids and another sequence that has five of nine identical amino acids, both of which he found to be "sufficient to potentially induce clinically relevant neuroinflammation." (*Id.* at 16.) Next, Dr. Steinman blasted the HPV16 L1 protein, found in both the Gardasil and Cervarix vaccines, and the hypocretin-2 receptor and found "various peptide sequences that are within [his] criteria." (*Id.* at 16-18.) Finally, Dr. Steinman blasted HPV11 L1 and HPV6

L1, both of which are only found in the Gardasil vaccine, and the hypocretin-2 receptor and found homologies in both that, in his opinion, were sufficient to cause clinically relevant neuroinflammation. (*Id.* 18-22.)

Dr. Steinman then turned to the FluMist vaccine. (Ex. 48, p. 5.) At first, he acknowledged that, originally, he found no mimics between hypocretin and the components of the FluMist. (*Id.* (citing Ex. 9, p. 22).) Instead, he explained that "the mimicry with . . . H1N1 has been shown to be with hypocretin-2 receptor and not hypocretin." (Ex. 40, p. 6 (citing Ahmed et al., *supra,* at Ex. 25; Roland S. Liblau, *Put to Sleep by Immune Cells,* NATURE (2018) (Ex. 43)).) However, after "focusing on the nucleoprotein of the 2013-2014 and 2014-2015 [flu] B components," Dr. Steinman found a molecular mimic that, in his opinion, "recognizes the same region in hypocretin that [he] described [..] as a mimic of HPV." (Ex. 48, p. 5.) Dr. Steinman described that he first performed a BLAST search and then "narrowed the search frame to only those areas of alignment of at least [five] amino acid[s] that were identical in a consecutive run of 12 or fewer amino acids." (*Id.* at 6-7 (citing Stephen F. Altschul et al., *Basic Local Alignment Search Tool*, 215 J. MOLECULAR BIOLOGY 403 (1990) (Ex. 50)).) Dr. Steinman defended his process and noted that a similar approach was used in a study by Robert Root-Bernstein. (*Id.* at 7 (citing Robert Root-Bernstein, *Rethinking Molecular Mimicry in Rheumatic Heart Disease and Autoimmune Myocarditis: Iaminin, Collagen IV, CAR, and B1AR as Initial Targets of Disease,* 2 FRONTIERS PEDIATRICS 1 (2014) (Ex. 51)).)

Dr. Steinman acknowledged that Duffy et al. found no association between the flu vaccine and narcolepsy, but stressed that they "assessed the incidence of narcolepsy in a population that was followed for approximately 30 years for its background rate but followed the post-vaccine population for [six] months (or a year). That created an artificially high background rate . . . which Duffy compared to an artificially low post-vaccine rate." (Ex. 48, p. 11 (citing (Jonathan Duffy et al., *Narcolepsy and Influenza A (H1N1) Pandemic 2009 Vaccination in the United States,* 83 NEUROLOGY 1823 (2014) (Ex. I)).) In addition, Dr. Steinman explained that Duffy et al., looked at the 2009 pandemic flu vaccine and the 2010-2011 flu vaccine, neither of which petitioner received in this case. (Ex. 40, p. 2.) Because flu vaccines change from year to year, Dr. Steinman argued that "epidemiological studies from one season or another can NOT be used as precedent for seasonal vaccines given in different years." (*Id.* at 3.) Finally, Dr. Steinman explained that he identified "a molecular mimic with the nucleoprotein of one of the [flu] B components of the FluMist vaccine, not the H1N1 component." (Ex. 48, p. 10.) Instead, Dr. Steinman relied on a study performed by Montplaisir et al., that found "an excess risk of approximately one case [of narcolepsy] per million vaccine doses, mainly in persons less than 20 years of age," and concluded that "a confounding effect of the [flu] infection cannot be ruled out." (*Id.* at 11 (Jacques Montplaisir et al., *Risk of Narcolepsy Associated with Inactivated Adjuvanted (AS03) A/H1N1 (2009) Pandemic Influenza Vaccine in Quebec,* 9 PUB. LIBR. SCI. ONE 1 (2014) (Ex. 52)).)

Dr. Steinman then cited a study that analyzed the blood of patients with both narcolepsy and cataplexy and found "autoreactive T cells to hypocretin" in patients with

narcolepsy. (Ex. 40, p. 1 (citing Daniela Latorre et al., *T Cells in Patients with Narcolepsy Target Self-Antigens of Hypocretin Neurons,* NATURE (2018) (Ex. 42)).) Specifically, Dr. Steinman explained that one of the mimics linking the HPV vaccination with narcolepsy that he identified through his BLAST searches was one of the peptide sequences identified by the article. (*Id.* at 4-6 (citing Latorre et al., *supra,* at Ex. 42).) He also compared the sequence he identified in the FluMist vaccine with both the paper by Latorre et al., and the Immune Epitope Database which "refer to this region of the FluMist vaccine that contains the molecular mimic of [hypocretin]." (Ex. 48, pp. 9-10 (citing Latorre et al., *supra,* at Ex. 42; IMMUNE EPITOPE DATABASE & TOOLS, https://www.iedb.org/ (last visited April 4, 2024)).) Dr. Steinman acknowledged that he chose to filter out negative results and show only positive results "because petitioner's theory is based on showing how there *are* molecular similarities between the components of the HPV vaccine and the antigens that stimulate T cells found in narcoleptic patients." (Ex. 53, p. 3.) Additionally, Dr. Steinman noted that his reliance on his Immune Epitope Database search is "just one component in a large body of peer reviewed literature that support this causation theory." (*Id.*)

Additionally, Dr. Steinman cited another study performed by Sakai et al., that found that "truncation of one proline in the sequence of myelin basic protein, led to stimulation of a different T cell clone that was still capable of inducing clinical paralysis and [experimental allergic encephalomyelitis]." (Ex. 48, p. 2 (citing Koichiro Sakai et al., *Involvement of Distinct Murine T-Cell Receptors in the Autoimmune Encephalitogenic Response to Nested Epitopes of Myelin Basic Protein,* 85 PROC. NAT'L ACADEMY SCI. 8608 (1988) (Ex. 49)).) Dr. Steinman noted that the sequence he identified through his BLAST searches is "contained in the epitope targeted by . . . T-cell[s] in the spinal fluid of a patient with narcolepsy," and contains a proline that could be the target as it was in the Sakai et al. study. (*Id.* at 3.) Dr. Steinman relied on this as evidence to support his belief that the only reason this sequence was not recognized by the T cells in Latorre et al. was because the sequence was missing a proline that had been shown to trigger T cells in other situations. (Ex. 53, pp. 1-2 (citing Sakai et al, *supra,* at Ex. 49).) Dr. Steinman explained that, while the other sequences in Latorre et al., did not share enough amino acids to meet his own criteria for a potential molecular mimic, the sequences in Latorre et al. "made overlapping peptides of length 20 in amino acids. The overlapping 20 amino acids contain a true epitope, but the 20 amino acids are NOT the actual epitope, only a nested group of amino acids are the actual epitope." (*Id.*) This is why a BLAST search is still required, to identify the actual epitope. (*Id.* at 2-3.) This also explained why Dr. Steinman's theory requires the addition of a proline to the sequence identified by the Latorre et al. article. (*Id.* (citing Latorre et al., *supra,* at Ex. 42).

Dr. Steinman acknowledged that short amino acid searches have been found to be a product of chance, however, he still found these searches to be "highly relevant." (Ex. 9, p. 23 (quoting Andre Silvanovich et al., *The Value of Short Amino Acid Sequence Matches for Prediction of Protein Allergenicity,* 90 TOXICOLOGICAL SCI. 252, 252 (2006) (Ex. 33, p. 1)).) He cited several studies that use smaller sequences than he does and still found that autoimmune disorders were induced, in his opinion, through

molecular mimicry. (*Id.* at 23-26.) For example, Dr. Steinman cited one study that induced paralysis in animals when these experimenters "passively transferred T cells that cross-reacted with myelin basic protein and HPV." (*Id.* at 23 (citing Rafael L. Ufret-Vincenty et al., *In Vivo Survival of Viral Antigen-Specific T Cells that Induce Experimental Auotimmune Encephalomyelitis,* 188 J. EXPERIMENTAL MED. 1725 (1998) (Ex. 34)).) Dr. Steinman acknowledged that molecular mimicry has been shown to be widespread, even if it is not causing autoimmune diseases. (*Id.* at 24.) He referenced another study that found T cells in healthy individuals were reactive to myelin basic protein. (*Id.* at 24-25 (citing Kohei Ota et al., *T-Cell Recognition of an Immuno-Dominant Myelin Basic Protein Epitope in Multiple Sclerosis,* 346 NATURE 183 (1990) (Ex. 35)).) Dr. Steinman also cites a study that found that "T cell lines could be isolated with 'comparable efficiency form MS patients and healthy individuals.'" (*Id.* at 25 (citing M. Pette et al., *Myelin Basic Protein-Specific T Lymphocyte Lines from MS Patients and Healthy Individuals,* 40 NEUROLOGY 1770 (1990) (Ex. 36)).) Thus, Dr. Steinman opined that while molecular mimicry is the key to understanding these autoimmune diseases, additional genetic and environmental factors may be necessary before a person develops an autoimmune disease. (*Id.* at 26.)

Finally, Dr. Steinman cited an epidemiological study that he indicates found an increased incidence rate of narcolepsy following the Gardasil vaccine. (Ex. 9, pp. 26-28 (citing Lisen Arnheim-Dahlstrom et al., *Autoimmune, Neurological, and Venous Thromboembolic Adverse Events After Immunisation of Adolescent Girls with Quadrivalent Human Papillomavirus Vaccine in Denmark and Sweden: Cohort Study,* 347 BRIT. MED. J. 1, 8 (2013) (Ex. 37, p. 8)).) Dr. Steinman acknowledged that the increased incidence rate was not statistically significant, but he still opined that this constitutes preponderant evidence that petitioner's vaccination could have caused her narcolepsy. (*Id.* at 28.)

Regarding the timing of petitioner's narcolepsy following her vaccination, Dr. Steinman opined that petitioner developed narcolepsy three months after her vaccinations and that this timeline is "consistent with what has been seen with [flu vaccine] related narcolepsy." (Ex. 9, p. 29.) In support of this conclusion, Dr. Steinman cited a systematic analysis of the incidence of narcolepsy in Finland from 2002-2010 and found an increase in narcolepsy up to eight months following vaccination with the Pandemrix flu vaccine. (*Id.* at 28 (citing Markku Partinen et al., *Increased Incidence and Clinical Picture of Childhood Narcolepsy Following the 2009 H1N1 Pandemic Vaccination Campaign in Finland,* 7 PUB. LIBR. SCI. ONE 1, 10 (2012) (Ex. 38, p. 10)).) Additionally, Dr. Steinman cited a retrospective review of children in England with narcolepsy who also received the Pandemrix flu vaccine. (*Id.* (citing Anne Marie Winstone et al., *Clinical Features of Narcolepsy in Children Vaccinated with AS03 Adjuvanted Pandemic A/H1N1 2009 Influenza Vaccine in England,* 56 DEVELOPMENTAL MED. & CHILD NEUROLOGY 1117 (2014) (Ex. 39)).) This study found onset of narcolepsy within three to 14 months following vaccination. (*Id.* (citing Winstone et al., *supra,* at Ex. 39).)

b. Respondent's expert, Maryann C. Deak, M.D., F.A.A.S.M.[6]

Respondent's first expert, Dr. Deak, submitted three expert reports in this case. (Exs. A, Z, II.) She opined that she did not "believe that petitioner's development of narcolepsy is related to either the FluMist or the HPV vaccination because of the lack of an established link between narcolepsy and either of these vaccinations, as well as a time course that does not support such an association." (Ex. A, p. 3.)

Dr. Deak summarized the criteria for narcolepsy type 1. (Ex. A, p. 4.) She noted that cataplexy is an "essential feature" of narcolepsy type 1 along with lapses into sleep, lapses in vigilance, nocturnal sleep disruption, hallucinations, and sleep paralysis. (*Id.* (citing AMERICAN ACADEMY OF SLEEP MEDICINE, INTERNATIONAL CLASSIFICATION OF SLEEP DISORDERS (3d ed. 2014) (Ex. E); Markku Partinen et al., *Narcolepsy as an Autoimmune Disease: The Role of H1N1 Infection and Vaccination,* 13 LANCET NEUROLOGY 600 (2014) (Ex. F)).) "Cataplexy is characterized by brief bilateral sudden loss of muscle tone while maintaining consciousness, which is precipitated by strong emotions." (*Id.*) Dr. Deak explained that narcolepsy "is caused by hypocretin deficiency, likely due to selective loss of hypocretin-producing neurons in the hypothalamus." (*Id.* (citing Emmanuel Mignot, *Narcolepsy: Genetics, Immunology, and Pathology,* in, PRINCIPLES AND PRACTICES OF SLEEP MEDICINE, NEUROLOGIC DISORDERS (Meir H. Kryger et al., eds., 6th ed., 2016) (Ex. G)).) Specifically, she explained that the "autoimmune hypothesis is the leading theory for the pathophysiology of narcolepsy type 1, largely due to a strong association of narcolepsy type 1 with human leukocyte antigen HLA DQB1*0602."[7] (*Id.* (citing Partinen et al., *supra,* at F; Mignot, *supra,* at Ex. G).) A potential association with the AS03-adjuvated H1N1 vaccine and the anti-streptococcal antibodies suggests environmental factors may also contribute to the development of narcolepsy. (*Id.* (citing

[6] Dr. Maryann Deak received her undergraduate degree and her medical degree from Georgetown University. (Ex. B, p. 2.) She completed a research fellowship in sleep medicine at Brigham and Women's Hospital at Harvard Medical School. (*Id.*; Ex. A, p. 1.) She completed two residencies in neurology, one at the University of Massachusetts and another at Yale University School of Medicine. (Ex. B, p. 2.) She is board certified in neurology and sleep medicine. (Ex. A, p. 1.) She currently works as the Associate Medical Director at eviCore Healthcare in the Division of Sleep Medicine and Neurology. (*Id.*; Ex. B, p. 1.) In this role, she "perform[s] clinical case reviews in sleep medicine and write[s] and review[s] clinical guidelines that impact the delivery of sleep medicine care nation-wide." (Ex. A, p. 1.) She selected six of her peer-reviewed publications that are included on her CV. (Ex. B, pp. 2-3.)

[7] Initially, Dr. Deak stressed that there is no "direct evidence of the autoimmune hypothesis." (Ex. A, pp. 4-5 (citing Shahrad Taheria, *The Immune Basis of Narcolepsy: What is the Evidence?,* 12 SLEEP MED. CLINIC 279 (2017) (Ex. C); Mignot, *supra,* at Ex. G).) Specifically, "neither auto-reactive T lymphocytes or autoantibodies specific to hypocretin peptides have been found." (*Id.* at 4 (citing Taheri, *supra,* at Ex. C; Mignot, *supra,* at Ex. G).) In fact, the only study that found hypocretin as an autoantigen was retracted because it could not be confirmed. (*Id.* (citing Partinen et al., *supra,* at Ex. F; Alberto K. De la Herran-Arita, *CD4$^+$ T Cell Autoimmunity to Hypocretin/Orexin and Cross-Reactivity to a 2009 H1N1 Influenza A Epitope in Narcolepsy,* 5 SCI. TRANSLATIONAL MED. 1 (2013) (retracted July 30, 2014) (Ex. 24)).) However, after Dr. Steinman introduced the Latorre, et al., paper, she later agreed that "the findings in this article strengthen the autoimmune hypothesis." (Ex. Z, p. 1 (citing Latorre et al., *supra,* at Ex. 42).) In any event, Dr. Deak agreed that type one narcolepsy is autoimmune and this acceptance is factored into the analysis below.

Emanuela Postiglione et al., *The Clinical Spectrum of Childhood Narcolepsy,* 38 SLEEP MED. REV. 70 (2018) (Ex. H)).) Narcolepsy has also occurred secondary to brain tumors, head trauma, or other conditions. (*Id.* at 5 (citing Postiglione et al., *supra,* at Ex. H).) However, most cases are idiopathic in nature. (*Id.* (citing Postiglione et al., *supra,* at Ex. H).)

Dr. Deak opined that there is no evidence that the HPV vaccination is associated with narcolepsy. (Ex. A, p. 5.) Dr. Deak explained that the epidemiological study cited by Dr. Steinman concluded there was no statistically significant association between the HPV vaccine and narcolepsy. (*Id.* (citing Arnheim-Dahlstrom et al., *supra,* at Ex. 37).) She disagreed with Dr. Steinman that the lack of a statistically significant finding could still be preponderant evidence that there is a causal relationship between the HPV vaccination and narcolepsy. (Ex. Z, p. 1)

Dr. Deak explained that "increased narcolepsy risk is specific to particular formulations of the H1N1 vaccine." (Ex. A, p. 5.) She acknowledged that the Pandemrix vaccine, an AS03-adjuvanted H1N1 vaccine, has been associated with an increased risk of narcolepsy. (*Id.* (citing Mignot, *supra,* at Ex. G); Ex. Z, p. 2 (citing Partinen et al., *supra,* at Ex. 38; Winstone et al., *supra,* at Ex. 39); Ex. II, p. 1 (citing Tomi O. Sarkanen et al., *Incidence of Narcolepsy After H1N1 Influenza and Vaccinations: Systematic Review and Meta-Analysis,* 38 SLEEP MED. REV. 177 (2018) (Ex. JJ)).) However, no similar increased incidence was found to be associated with the H1N1 vaccine with a different adjuvant that was given in the United States. (Ex. A, p. 5.) In support of this conclusion, Dr. Deak cited a population-based cohort study that concluded that the H1N1 vaccine administered in the United States was "not associated with an increased risk of narcolepsy." (Duffy et al., *supra,* at Ex. I, p. 1.) She explained that the study she cited, Duffy et al., "is relevant because it examines non-adjuvanted H1N1 vaccine that was administered in the United States." (Ex. Z, p. 2 (citing Duffy et al., *supra,* at Ex. I).) This study also examined a vaccine that contained the same adjuvant "but utilized a different process to isolate surface antigen," that was also associated with an increased risk of narcolepsy, although less than the Pandemrix. (*Id.* (citing Mignot, *supra,* at Ex. G).) Additionally, Dr. Deak notes that the 2013-2014 and 2014-2015 flu vaccines that are relevant in this case contain similar components to the 2009 and 2010-2011 flu vaccines studied in Duffy et al. (*Id.* (citing FDA, *Lot Release (Biologics): Influenza Virus Vaccine for the 2013-2014 Season,* Ex. 16; FDA, *Lot Release (Biologics) Influenza Virus Vaccine for the 2014-2015 Season,* Ex. 17; Duffy et al., *supra,* at Ex. I; Mignot, *supra,* at Ex. G).)

Additionally, Dr. Deak cited a literature review that found "a lower risk of narcolepsy . . . detected in Canada after Arepanrix, an AS03-adjuvated H1N1 vaccine," and that there was "no increased risk" reported for nonadjuvanted H1N1 vaccines. (Ex. A, p. 5 (citing Xuan-Hung Nguyen et al., *Vaccine-Associated Inflammatory Diseases of the Central Nervous System: From Signals to Causation,* 29 CURRENT OP. NEUROLOGY 1, 5 (2016) (Ex. J, p. 5)).) Dr. Deak opines that "[t]he evidence Dr. Steinman presents linking FluMist to narcolepsy is solely based on his own BLAST searches," and that

"there is no evidence of an association between the vaccines in question in this case and an increased risk of narcolepsy." (Ex. II, p. 1.)

Dr. Deak acknowledged that the Latorre et al., article does strengthen Dr. Steinman's hypothesis, however, she explained that "there remain many unanswered questions regarding the hypocretin-specific T cells described," and she explained that she believed further studies were needed to confirm this hypothesis. (Ex. Z, p. 1.) Additionally, she explained that "[t]he authors did not find cross-reactivity with 2009 [flu] vaccine containing H1N1," and, therefore, this article does not necessarily support petitioner's theory of molecular mimicry causation as it pertains to the flu vaccine. (Ex. Z, p. 1 (citing Latorre et al., *supra,* at Ex. 42); Ex. II, p. 1 (citing Latorre et al., *supra,* at Ex. 42).)

Regarding the time between petitioner's vaccination and the onset of her narcolepsy symptoms, Dr. Deak explained that narcolepsy symptoms take time to develop and that between usually 11 and 12 weeks or even up to a year "would have passed before the manifestation of her first symptoms." (Ex. A, p. 3; Ex. Z, p. 2 (citing Kiran Maski et al., *Listening to the Patient Voice in Narcolepsy: Diagnostic Delay, Disease Burden, and Treatment Efficacy,* 13 J. CLINICAL SLEEP MED. 419 (2017) (Ex. BB); Emma Morrish et al., *Factors Associated with a Delay in the Diagnosis of Narcolepsy,* 5 SLEEP MED. 37 (2004) (Ex. D); Yves Dauvilliers et al., *Narcolepsy with Cataplexy,* 369 LANCET 499 (2007) (Ex. CC)).) Dr. Deak acknowledged that Dr. Steinman relied on two retrospective studies to support his conclusion that petitioner's narcolepsy occurred within a reasonable timeframe after her vaccination. (Ex. A, p. 3 (citing Partinen et al., *supra,* at Ex. 38; Winstone et al., *supra,* at Ex. 39).) However, Dr. Deak noted that both of these studies involved the Pandemrix vaccine, which has "never been administered in the United States, and the petitioner did not receive." (*Id.*) Additionally, Dr. Deak explained that both of these studies "refer to an increased risk of narcolepsy in children," and specifically, the study from Finland found no increased incidence of narcolepsy in adults 20 years or older. (*Id.* at 4 (citing Partinen et al., *supra,* at Ex. 38; Winstone et al., *supra,* at Ex. 39); Ex. II, p. 1 (citing Partinen et al., *supra,* at Ex. 38; Winstone et al., *supra,* at Ex. 39).) Finally, Dr. Deak described how retrospective studies are "difficult to assess" because of "the frequent delay between symptom onset and diagnosis." (Ex. A, p. 4 (citing Taheria, *supra,* at Ex. C; Morrish et al., *supra,* at Ex. D).) Therefore, Dr. Deak opined that the evidence that petitioner developed narcolepsy in a medically appropriate time frame is "lacking." (*Id.*) However, Dr. Deak acknowledged that there is a better sense of timing in this case because cataplexy was present early in the course of petitioner's symptom development and petitioner saw her physicians often. (Ex. Z, p. 3; Ex. II, pp. 1-2.)

c. Respondent's expert, Neil Romberg, M.D.[8]

Respondent's second expert, Dr. Romberg, also submitted three reports in this case. (Exs. K, Y, DD.) Dr. Romberg noted that while "molecular mimicry is often employed to explain a variety of autoimmune diseases, it is a theory considered by immunological experts to be largely unproven and arguably, in most cases, to be unprovable." (Ex. K, p. 2 (citing Christophe Benoist & Diane Mathis, *Autoimmunity Provoked by Infection: How Good is the Case for T Cell Epitope Mimicry?,* 2 NATURE IMMUNOLOGY 797 (2001) (Ex. M); Lori J. Albert & Robert D. Inman, *Molecular Mimicry and Autoimmunity,* 341 NEW ENG. J. MED. 2068 (1999) (Ex. N)).) Dr. Romberg noted that authors discussing theories like molecular mimicry are careful to acknowledge that these mechanisms are hypotheses. (Ex. Y, p. 2 (citing Fujnami et al., *Molecular Mimicry, Bystander Activation, or Viral Persistence: Infections and Autoimmune Disease,* 19 CLINICAL MICROBIOLOGY REV. 80, 87 (2006) (Ex. 45, p. 7); LouAnn Barnett et al., *Virus Encoding an Encephalitogenic Peptide Protects Mice From Experimental Allergic Encephalomyelitis,* 64 J. NEUROIMMUNOLOGY 163 (1996) (Ex. Y, Tab 1); Urs Christen et al., *Cure of Prediabetic Mice by Viral Infections Involves Lymphocyte Recruitment Along an IP-10 Gradient,* 113 J. CLINICAL INVESTIGATION 74 (2004) (Ex. Y, Tab 2); Urs Christen et al., *A Dual Role for TNF-α in Type 1 Diabetes: Islet-Specific Expression Abrogates the Ongoing Autoimmune Process When Induced Late but Not Early During Pathogenesis,* 166 J. IMMUNOLOGY 7023 (2001) (Ex. Y, Tab 3)).) Dr. Romberg concluded that these examples undermine Dr. Steinman's position that the "HPV vaccine or FluMist vaccine cross-activated, not depleted, orexin specific T cells to cause autoimmune disease." (*Id.*) He explained that before molecular mimicry is considered as a cause of an autoimmune disorder, certain criteria should be met. (Ex. K, p. 3 (citing Benoist & Mathis, *supra,* at Ex. M; C. Win Ang et al., *The Guillain-Barre Syndrome: A True Case of Molecular Mimicry,* 25 TRENDS IMMUNOLOGY 61 (2004) (Ex. O)).)

The first criteria requires the "[e]stablishment of an epidemiologic association between the vaccine antigen and the immune mediated disease." (Ex. K, p. 3.) Dr. Romberg explained that Dr. Steinman relied on one epidemiological study that found a slight increase in the incidence of narcolepsy following HPV vaccination. (*Id.* (citing Arnhein-Dalstrom et al., *supra,* at Ex. 37).) While Dr. Steinman opined that the slight increased incidence is preponderant evidence, Dr. Romberg disagreed, and explained that the incidence rates included in this study are raw numbers, "not adjusted for

[8] Dr. Neil Romberg received his undergraduate degree from the University of Michigan and his medical degree from Pennsylvania State College of Medicine. (Ex. L, p. 1.) He completed his residency in pediatrics at New York University School of Medicine and an Allergy and Clinical Immunology Fellowship at Yale University. (*Id.*; Ex. K, p. 1.) He is board certified in Allergy and Clinical Immunology. (Ex. K, p. 1.) He currently works as an assistant professor of Pediatrics at the University of Pennsylvania and an attending physician at the Children's Hospital of Philadelphia. (*Id.*) He explained that "[t]he focus of [his] career has been to care for patients with inherited immunological disorders and to investigate the molecular mechanisms that underlie their diseases." (*Id.*) Specifically, Dr. Romberg "investigates several topics in human immunology including topic[s] relevant to this case including regulatory T cells, T-cell activation, breaks in immune tolerance and the genetic basis of inflammatory diseases." (*Id.*) Dr. Romberg listed six peer-reviewed publications on his CV. (Ex. L, p. 2.)

confounding variables." (*Id.*) The authors "also calculated an adjusted rate ratio" accounting for those variables which include "country, age, calendar year, and parental country of birth." (*Id.* (citing Arnhein-Dalstrom et al., *supra,* at 37).) When adjusted based on these variables, the incident rate drops even further. (*Id.* (citing Arnhein-Dalstrom et al., *supra,* at Ex. 37, p. 10).) Therefore, Dr. Romberg concluded that this study supported the conclusion that "HPV vaccination and narcolepsy are independent, unrelated events that only randomly co-occur." (*Id.*)

The second criteria requires the "[i]dentification of autoreactive T cells or autoantibodies that recognize a human structure (target antigen) that if perturbed could explain symptomology." (Ex. K, p. 3.) Dr. Romberg addressed Dr. Steinman's conclusion that the hypocretin-2 receptor was the potential target in petitioner's case. (*Id.* at 3-4.) He explained that there is no evidence in petitioner's medical records that she had autoantibodies or autoreactive T cells targeting these receptors, however, Dr. Romberg also noted that this testing is currently clinically impossible. (*Id.* at 3.) Additionally, Dr. Romberg noted that it has not been proven that these receptors contribute to narcolepsy. (*Id.* (citing De la Herran-Arita, *supra,* at Ex. 24; Ahmed et al., *supra,* at Ex. 25).) Dr. Romberg also explained that specific HLA alleles have also been associated with narcolepsy. (*Id.* at 3-4 (citing Taku Miyagawa et al., *Variant Between CPT1B and CHKB Associated with Susceptibility to Narcolepsy,* 40 NATURE GENETICS 1324 (2008) (Ex. Q)).) Dr. Romberg acknowledged that the Latorre et al., study was "the first convincing evidence that [he has] seen to suggest that narcolepsy may be an autoimmune condition." (Ex. Y, p. 2 (citing Latorre et al., *supra,* at Ex. 42).) However, he noted that a similar study was retracted "because the results could not be reproduced." (*Id.* (citing De la Herran-Arita, *supra,* at Ex. 24).) Therefore, he is hesitant to accept this study without replicability. (*Id.*)

The third criteria requires the "[i]dentification of a vaccine antigen that is molecularly similar to the target antigen." (Ex. K, p. 4.) On this point, Dr. Romberg opined that "it is very unlikely that the weak similarities between the HPV L1 and MBP protein segments identified by Dr. Steinman are sufficient to cause pathologic cross reactivity." (*Id.*) Dr. Romberg highlighted two problems with Dr. Steinman's BLAST methodology. (*Id.*) "First the human orexin/orexin-2[9] receptor protein segments identified by Protein BLAST were chosen entirely upon Dr. Steinman's lenient homology criteria." (*Id.*) Dr. Romberg addressed the publications cited by Dr. Steinman to support his contention that T cells "recognize polypeptides only sharing [five] of 12 or [four] of 11 amino acid residues with" the protein, therefore, sequences of this length are enough to trigger molecular mimicry. (Ex. DD, p. 2 (citing Gautam et al., *supra,* at Ex. 31; Gautam et al., *supra,* at Ex. 32).) Dr. Romberg explained that there are an "enormous number of polypeptides that share [five] of 12 or [four] of 11 sequential but non-consecutive amino acids." (*Id.*) Therefore, Dr. Romberg opined that Dr. Steinman's process "vastly expands the number of sequences he considers 'sufficient to potentially induce clinically relevant neuroinflammation.'" (*Id.* at 2-3.) Therefore, Dr. Romberg explained that Dr.

[9] Hypocretin and orexin are used interchangeably to refer to the same protein and protein receptor. Dr. Romberg uses them interchangeably, and I will also use them interchangeably for the purposes of this summary.

Steinman "chooses to focus his report on one or two sequences that he claims support his theory of causation but the ignores a pool of millions that do not." (*Id.* at 3.)

"Secondly, the identified orexin/orexin-2 receptor protein segments are ubiquitous in nature." (Ex. K, p. 5.) He also explained that generated BLAST searches are associated with an Expect (E) value[10]. (*Id.* at 4; Ex. DD, pp. 1-2.) Dr. Romberg reported that all the E values assigned to Dr. Steinman's BLAST searches were high, meaning it was likely these similarities were due to chance. (Ex. K, p. 4.) Dr. Romberg ran his own BLAST search and found "distinct microbial protein[s] with greater homology to the orexin/orexin-2 receptor segments than any of the HPV L1 protein[s]." (*Id.* at 5.) Dr. Romberg makes two conclusions based on Dr. Steinman's BLAST searches: (1) "an immune response targeting the identified orexin and the orexin-2 receptor protein segments would more likely be due to" homology between microbes than the HPV vaccine; and (2) "[t]he orexin and orexin-2 receptor protein segments Dr. Steinman identified are unlikely to be highly immunogenic in any pathogenically meaningful way and molecularly mimicked." (*Id.*)

Additionally, Dr. Romberg explained that the Latorre et al., article identified three amino acid sequences, two in HPV11 L1 and one in a flu nucleoprotein, that shared some sequences with hypocretin, however, the "authors used overlapping peptides to map which orexin epitopes were recognized" by reactive T cells found in narcoleptic patients. (Ex. Y, p. 2 (citing Latorre et al., *supra,* at Ex. 42).) Dr. Romberg noted that Latorre et al., found two peptides, however, his own BLAST searches "failed to identify any areas of similarity" between the peptides identified in the study and proteins in the HPV vaccine. (*Id.*) While Dr. Steinman found similarity between one of the proteins he identified in his own BLAST search and the peptides identified in the study, Dr. Romberg again opined that "Dr. Steinman's homology criteria is much too lenient to intuit cross-reactivity in a meaningful way." (*Id.* at 3.) The first HPV11 L1 sequence met the criteria identified by Dr. Steinman with four out of nine amino acids matching the hypocretin sequence, however, it was not recognized by narcoleptic T cells. (Ex. DD, p. 3 (citing Latorre et al., *supra,* at Ex. 42).) This was the sequence Dr. Steinman identified as the potential molecular mimic. (Ex. 40, p. 5.) The second HPV11 L1 sequence and the flu sequence did not meet Dr. Steinman's criteria, however, were recognized by narcoleptic T cells. (Ex. DD, p. 3 (citing Latorre et al., *supra,* at Ex. 42).) Dr. Steinman opined that this is because the second two sequences contain one specific proline, however, Dr. Romberg disagreed and opined that the polypeptide chains recognized by the narcoleptic T cells "likely contains the essential recognition sequence," and the sequence relied on by Dr. Steinman does not. (Ex. DD, p. 3.) Dr. Romberg summarized his findings in a chart:

[10] Dr. Romberg explained in his expert report that the Expect value (or E value) is "assigned to any two paired protein segments" and "describes how likely that [a] match could be due to chance." (Ex. K, p. 4.) Low E values (<0.00001) "denote significant protein segment similarity that [are] unlikely to be random," and high E values (>1) "denote a low degree of similarity that cannot be reliably differentiated from a random pairing." (*Id.*)

Peptide #	Peptide sequence	T-cell recognition?
1	NHAAGILTMGRRAGAEPAPR	not recognized
2	MGRRAGAEPAPRPCLGRRCS	recognized
3	PAPRPCLGRRCSAPAAASVA	recognized
4	LGRRCSAPAAASVAPGGQS(	not recognized

(Ex. Y, p. 2.)

Dr. Romberg additionally addressed Dr. Steinman's reliance on the Immune Epitope Database. (Ex. DD, pp. 4-10.) He explained that the Immune Epitope Database was created "to facilitate the development of vaccines and drugs that target emerging infections and bioterrorism pathogens." (*Id.* 4 (citing Bjoern Peters et al., *The Immune Epitope Database and Analysis Resource: From Vision to Blueprint,* 3 PUB. LIBR. SCI. BIOLOGY e91 (2005) (Ex. FF)).) He noted that the program "simplifies reporting by listing assays as positive, i.e. supportive of immune recognition, or negative." (*Id.*) He explained that there are various ways of narrowing or broadening a search through this website. (*Id.*) Dr. Romberg then addressed Dr. Steinman's search criteria. (*Id.*) First, Dr. Romberg reported that Dr. Steinman's input sequence was for an hypocretin nucleoprotein that only shares five out of 10 amino acids with HPV11 L1. (*Id.*) Additionally, Dr. Steinman set the stringent filter to 70%, broadening his search, and "elected to suppress all sequences without positive data from his query results." (*Id.*) Dr. Romberg ran a similar search, however, he elected to include both positive and negative results, which returned six additional searches to the ones identified by Dr. Steinman's search. (*Id.* at 5.) Dr. Romberg noted that one result identified the sequence relied on by Dr. Steinman in his previous report, however, that sequence was not immunogenic. (*Id.* at 6 (citing Melanie Ramberger et al., *CD4⁺ T-Cell Reactivity to Orexin/Hypocretin in Patients with Narcolepsy Type 1,* 40 SLEEP 1 (2017) (Ex. GG)).)

Dr. Romberg performed his own Immune Epitope Database search using more stringent search criteria, including a strict substring filter and permitting both positive and negative assays. (Ex. DD, pp. 6-9.) Dr. Romberg identified a sequence that "shares [five] of 10 non-identical amino acids with [flu] NP and HPV11 L1." (*Id.* at 6.) Dr. Romberg noted that this sequence was analyzed in two assays as part of one study, one positive and one negative. (*Id.* at 7 (citing Guo Luo et al., *Autoimmunity to Hypocretin and Molecular Mimicry to Flu in Type 1 Narcolepsy,* 115 PROC. NAT'L ACADEMY SCI. E12323 (2018) (Ex. HH)).) However, after analyzing the information provided by the study, Dr. Romberg opined that "the positive assay cited by the Immune Epitope Database does not strongly support [the sequence] to be an immune epitope. In fact, there is a case to be made that [the sequence] recognizing T cells occur[s] so infrequently that the [Immune Epitope Database] should recategorize the description of Lou et al.'s T cell results as a 'negative assay.'" (*Id.* at 9.) Additionally, "the frequency of [the sequence] recognizing T cells appear[s] to be similar in Pandemrix vaccinated healthy controls and narcoleptic patients." (*Id.*)

The fourth and final criteria requires "[r]eproduction of the disease in an animal model." (Ex. K, p. 5.) Dr. Romberg noted that Dr. Steinman relied on experimental autoimmune encephalitis mouse models to satisfy this criteria. (*Id.*) However, Dr.

Romberg explained that "narcolepsy is not a demyelinating disease and its status as an inflammatory disease is controversial," therefore, experimental autoimmune encephalitis "is not a useful lens to view narcolepsy." (*Id.*) Animal models of narcolepsy "include chemical ablation of orexin cells with saporin," an immune suppressant, however, they do not include narcolepsy with an autoimmune pathology. (*Id.* (citing Lichao Chen et al., *Animal Models of Narcolepsy,* 8 CENT. NERVOUS SYS. & NEUROLOGICAL DISORDERS 296 (2009) (Ex. T)).) Dr. Romberg opined that the fact that an immune suppressant aggravates, instead of alleviates, canine cataplexy is further evidence that narcolepsy is "not inflammatory in nature." (*Id.* (citing Takashi Kanbayashi et al., *Thalidomide, a Hypnotic with Immune Modulating Properties, Increases Cataplexy in Canine Narcolepsy,* 7 NEUROREPORT 1881 (1996) (Ex. U)).)

Dr. Romberg also addressed Dr. Steinman's theory as to the onset of petitioner's narcolepsy following her vaccinations. (Ex. K, p. 6.) Dr. Romberg noted that petitioner had both received previous flu vaccinations, with similar compositions to that of her 2014 vaccination, and had "been exposed to HPV through natural infection." (*Id.* (citing Ex. 1, pp. 202, 1767).) Therefore, Dr. Romberg opined that if her vaccinations had been responsible for her narcolepsy, the proteins she had been exposed to previously should have triggered her narcolepsy after earlier exposures. (*Id.*) Therefore, Dr. Romberg opined that "[t]he most obvious explanation is that HPV infection and vaccination are wholly unrelated to narcolepsy." (*Id.*)

V. Analysis

As discussed above, petitioner's burden of proof in a cause-in-fact claim is to meet the three-part *Althen* test, which includes (1) a general theory of causation implicating the vaccine as a cause of the alleged condition, (2) a logical sequence of cause and effect implicating the vaccination as a cause of petitioner's own condition, and (3) appropriate timing of onset based on the theory of causation. 418 F.3d at 1278. For the reasons discussed below, the outcome of this case turns on the first *Althen* prong, petitioner's general theory of causation.

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 (quoting *Pafford,* 2004 WL 1717359, at *4). Such a theory must only be "legally probable, not medically or scientifically certain." *Knudsen,* 35 F.3d at 548-49. 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. *See Andreu*, 569 F.3d at 1378-79 (citing *Capizzano,* 440 F.3d at 1325-26). However, "[a] petitioner must provide a 'reputable medical or scientific explanation' for [her] theory. While it does not require medical or scientific certainty, it must still be 'sound and reliable.'" *Boatmon,* 941 F.3d at 1359 (quoting *Knudsen*, 35 F.3d at 548-49).

a. *Althen* Prong One is Dispositive

Because I have concluded that petitioner has not demonstrated that either the flu or HPV vaccines at issue in this case likely can cause narcolepsy, it is not necessary to address in detail whether the conditions did so in this particular case. Given the outcome regarding *Althen* prong one, by definition they likely did not. Thus, I do not separately reach *Althen* prongs two and three in this decision. However, I do briefly note that, had petitioner satisfied *Althen* prong one, then it is possible she may have prevailed under *Althen* prongs two and three.

Regarding *Althen* prong two, there is no disagreement between the experts that petitioner was properly diagnosed with narcolepsy. (*See* Ex. 9, p. 6; Ex. A, p. 3; Ex. K, p. 2.) Additionally, petitioner's medical records are sufficient to demonstrate that she suffered narcolepsy with cataplexy. (*See* Ex. 1, p. 756; Ex. 4, pp. 8-9.) This establishes her narcolepsy as type one narcolepsy. (AMERICAN ACADEMY OF SLEEP MEDICINE, *supra,* at Ex. E, p. 3; Partinen et al., *supra,* at Ex. F, p. 1).) Accordingly, petitioner has preponderantly established that she suffered the autoimmune form of narcolepsy. Respondent raises the fact of petitioner's pre-existing HPV infection as a reason to question whether the HPV vaccine would have been a cause of narcolepsy under Dr. Steinman's theory; however, he has not actually substantiated that petitioner's HPV infection is a cause of her condition. (ECF No. 79, p. 22; Ex. K, p. 6.)

Further to this, petitioner's treating physician, Dr. Htoo, opined that petitioner's narcolepsy was "likely triggered" by her FluMist vaccine. (Ex. 1, p. 1184.) Had Dr. Steinman's theory of causation been accepted, the fact of this opinion may have further buttressed his causal opinion under *Althen* prong two – at least as far as the FluMist would be concerned. However, the basis for Dr. Htoo's opinion is not stated. Moreover, Dr. Htoo does not identify any factor supporting this conclusion other than a potential temporal relationship. (*Id.* at 1180-81.) The Federal Circuit has explained that "[a]lthough probative, neither a mere showing of a proximate temporal relationship between vaccination and injury, nor a simplistic elimination of other potential causes of the injury suffices, without more, to meet the burden of showing actual causation." *Althen*, 418 F.3d at 1278 (citing *Grant*, 956 F.2d at 1149). Thus, "[a] treating physician's recognition of a temporal relationship does not advance the analysis of causation." *Isaac v. Sec'y of Health and Human Servs*., No. 08-601V, 2012 WL 3609993, at *26 (Fed. Cl. Spec. Mstr. July 30, 2012). Accordingly, Dr. Htoo's opinion, though relevant as some evidence regarding *Althen* prong two, does not add preponderant support to petitioner's claim.

Regarding *Althen* prong three, the experts agree that petitioner suffered onset of her condition in April of 2014, approximately three months post-vaccination. (*See* Ex. 9, pp. 28-29; Ex. A, p. 3; Ex. K, pp. 2, 6.) In asserting that this is an appropriate period of onset to infer vaccine causation, Dr. Steinman cites two epidemiologic studies examining incidences of narcolepsy following administration of the Pandemrix H1N1 flu vaccine. (Ex. 9, p. 28 (citing Partinen et al., *supra,* at Ex. 38; Winstone et al., *supra,* at Ex. 39).) As discussed below, the causal relationship between the Pandemrix vaccine

and narcolepsy is undisputed. (*See Id.* (citing Partinen et al., *supra,* at Ex. 38; Winstone et al., *supra,* at Ex. 39); Ex. A, p. 5 (citing Mignot, *supra,* at G.).) Respondent's experts also do not dispute that the studies cited by Dr. Steinman support a three-month latency as appropriate, but they do challenge the relevance of the studies, particularly given that they address a completely different vaccine. (Ex. A, p. 3-4 (citing Partinen et al., *supra,* at Ex. 38; Winstone et al., *supra,* at Ex. 39).) Although a three month latency is longer than what is usually expected for an autoimmune condition to manifest post-vaccination,[11] narcolepsy is particularly known for having an insidious onset. Because I have concluded that petitioner has not shown the vaccinations at issue can cause narcolepsy in the same manner as the Pandemrix vaccine, I agree with respondent's experts that these studies are not helpful. However, had Dr. Steinman's opinion been persuasive under *Althen* prong one, it is not clear that his reliance on Pandemrix studies vis-à-vis timing of onset would otherwise be unreasonable. *Pierson v. Sec'y of Health & Human Servs.,* No. 17-1136V, 2022 WL 322836, at *32 (Fed. Cl. Spec. Mstr. Jan. 19, 2022); *Cooper v. Sec'y of Health & Human Servs.,* No. 18-1885V, 2024 WL 1522331, at * 18-20 (Fed. Cl. Spec. Mstr. Mar. 12, 2024).

In sum, the evidence pertinent to *Althen* prongs two and three is not robust, but petitioner's own circumstances are consistent with what would seem to be expected under Dr. Steinman's theory of causation, suggesting petitioner might have satisfied *Althen* prongs two and three if she had succeeded under *Althen* prong one. Conversely, however, and especially given the limitations of the treating physician opinion, the fact that petitioner's narcolepsy manifested three months following her vaccination does not in itself lend any further credence to petitioner's theory under *Althen* prong one. *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).

b. Molecular Mimicry is a Sound Concept but It Is Not Demonstrated by BLAST Search Results Alone

In this case, there is no debate between the experts that narcolepsy is an autoimmune condition. (*See* Ex. 9, pp. 7-8; Ex. K, pp. 3-4, 1; Ex. Z, p. 1.) However, the fact that narcolepsy is autoimmune does not imply that it is vaccine caused without more. Thus, as with many cases in the program, petitioner's theory of causation asserts that autoimmune narcolepsy can be shown to be vaccine caused via the concept of molecular mimicry. (*See* Exs. 9, 40, 48, 53.)

As Dr. Romberg stressed, molecular mimicry is a concept with several constituent parts that must be demonstrated. Specifically, it involves (1) a susceptible host (2) encounters a foreign antigen that has sufficient similarity ("homology") with

[11] For example, it has previously been noted that special masters do not generally attribute vaccine causation to autoimmune demyelinating conditions after 60 days post-vaccination. *See Barone v. Sec'y of Health & Human Servs.,* No. 11-707V, 2014 WL 6834557, at *13 (Fed. Cl. Spec. Mstr. Nov. 12, 2014) (citing *Aguayo v. Sec'y of Health & Human Servs.,* No. 12-563V, 2013 WL 441013, at *3 (Fed. Cl. Spec. Mstr. Jan 15, 2013); *Corder v. Sec'y of Health & Human Servs.,* No. 08-228V, 2011 WL 2469736, at *27-29 (Fed. Cl. Spec. Mstr. May 31, 2011).

components of host tissue such that (3) the immune system "cross reacts," producing antibodies that attack the host tissue instead of the foreign antigen to (4) ultimately cause disease or injury. (Ex. K.) Molecular mimicry "is a generally accepted scientific principle, [but] mere invocation of the scientific term does not carry a petitioner's burden in a Program case." *Deshler v. Sec'y of Health & Human Servs*., No. 16-1070V, 2020 WL 4593162, at *20 (Fed. Cl. Spec. Mstr. July 1, 2020) (citing *Forrest v. Sec'y of Health & Human Servs.*, No. 14-1046V, 2019 WL 925495, at *3 (Fed. Cl. Spec. Mstr. Jan. 18, 2019)). This is because, as respondent's expert has stressed (Ex. K, pp. 4-5; Ex. Y, p. 1; Ex. DD, p. 1) and Dr. Steinman has agreed (Ex. 40, p. 3), "the finding of sequence homology does not necessarily mean the similarity has significance to the immune system." *Tullio v. Sec'y of Health & Human Servs.*, No. 15-51V, 2019 WL 7580149, at *15 (Fed. Cl. Spec. Mstr. Dec. 19, 2019), *aff'd,* 149 Fed. Cl. 448 (2020); *see also Caredio ex rel. D.C. v. Sec'y of Health & Human Servs.,* No. 17-0079V, 2021 WL 4100294, at *31 (Fed. Cl. Spec. Mstr. July 30, 2021) ("*demonstration of homology alone is not enough to establish a preponderant causation theory*") (emphasis in original) (citing *Schultz v. Sec'y of Health & Human Servs.,* No. 16-539V, 2020 WL 1039161, at *22 n. 24 (Fed. Cl. Spec. Mstr. Jan. 24, 2020)), *mot. for rev. denied,* 2021 WL 6058835 (Fed. Cl. Dec. 3, 2021).

However, petitioners in this program are not required to demonstrate scientific certainty. Therefore, prior cases have expressed with regard to the application of molecular mimicry that "[t]he line must be drawn somewhere between speculation and certainty." *Brayboy v. Sec'y of Health & Human Servs.,* No. 15-183V, 2021 WL 4453146, at *19 (Fed. Cl. Spec. Mstr. Aug. 30, 2021). For example, in *Brayboy*, an omnibus proceeding addressing autoimmune premature ovarian insufficiency, the special master found it sufficient that the petitioners "identified cross-reaction between components of the vaccine and proteins in the body that are directly responsible for the health and productivity of the organ at issue" and further expressed that requiring further steps, or insisting on direct, testable evidence, would impermissibly heighten the petitioners' burden of proof. *Id*. Thus, I have in prior instances credited Dr. Steinman's opinions where he has cited circumstantial evidence beyond homology to demonstrate molecular mimicry. *Pierson,* 2022 WL 322836, at -*27-31; *Cooper,* 2024 WL 1522331, at * 13-18; *but see A.T. v. Sec'y of Health & Human Servs.,* No. 16-393V, 2021 WL 6495241, at *23-25 (Fed. Cl. Spec. Mstr. Dec. 17, 2021).

Here, the core element of Dr. Steinman's molecular mimicry theory is his purported demonstration via "BLAST" search results of homology between the antigens contained in the subject vaccinations and orexin, which is implicated in the autoimmune disease process of narcolepsy. (*See* Exs. 9, 40, 48, 53.) Respondent's experts have presented detailed criticisms regarding Dr. Steinman's reliance on BLAST searches as evidence of molecular mimicry and his specific methodology in producing his results. However, it is not necessary to address those finer criticisms given the fundamental limitations of the resulting evidence. Dr. Steinman's BLAST searches have, in some cases, complemented other evidence of record otherwise suggestive of a causal

relationship.[12] However, these findings are limited and not strong evidence.[13] Even if I agree that it is theoretically *possible* that the short sequence homologies that Dr. Steinman has identified could ultimately be shown to be meaningful in a given case, merely demonstrating a possible theory of causation is not petitioner's burden of proof. *Boatmon,* 941 F.3d at 1360.

In his first report, Dr. Steinman suggests that because the BLAST results he has generated "are not inevitable" they are therefore "highly relevant." (Ex. 9, p. 23.) However, this is not so. The fact that chance homologies are not inevitable for any given BLAST search does not mean that every match that occurs is therefore meaningful. Even though Dr. Steinman has presented experimental evidence purporting to show that a short sequence homology of 5 out of 12 amino acids can induce experimental allergic encephalomyelitis (*Id.* at 8-11 (citing Gautam et al., *supra,* at Ex. 31; Gautam et al., *supra,* at Ex. 32)), Dr. Romberg is persuasive on respondent's behalf in explaining that the E values for the BLAST results Dr. Steinman has actually generated are such that these results have a high likelihood of merely being due to

[12] *See e.g. Henkel v. Sec'y of Health & Human Servs.,* No. 15-1048V, 2022 WL 16557979, at *39-40 (Fed. Cl. Spec. Mstr. Aug. 31, 2022) (finding that "a five-out-of-ten match, by a preponderance of evidence, could result in molecular mimicry," and that Dr. Steinman's reliance on the Latorre article is persuasive), *mot. rev' den'd,* 165 Fed. Cl. 153 (2023); *Cobb v. Sec'y of Health & Human Servs.,* 17-1123V, 2023 WL 6457568, at *19 (Fed. Cl. Spec. Mstr. Aug 21, 2023) (finding that Dr. Steinman "demonstrated that the orexin peptide targeted in type 1 narcolepsy has sequence homology with a component of the Gardasil vaccine" relying on a homology identified by Dr. Steinman's BLAST search and the Latorre article); *Sparrow v. Sec'y of Health & Human Servs.,* No. 18-295V, 2024 WL 1599165, at *24 (Fed. Cl. Spec. Mstr. Mar. 19, 2024) (finding that, in this case, respondent has provided "relatively little evidence that BLAST was an improper tool"); *E.M. v. Sec'y of Health & Human Servs.,* No. 14-753V, 2021 WL 3477837, at *38 (Fed. Cl. Spec. Mstr. July 9, 2021) (finding that "Dr. Steinman's molecular mimicry theory and identified sequence homologies have been sufficiently developed and largely unrebutted").

[13] *See e.g. E.S. v. Sec'y of Health & Human Servs.,* 17-480V, 2020 WL 9076620, at *45 (Fed. Cl. Spec Mstr. Nov. 13, 2020) (observing that "merely showing via BLAST searches that some homology exists between amino acid sequences in the HPV vaccine and components and nerve cells does not amount to a preponderant showing that the vaccine can produce antibodies that will cross-react against those cells"), *mot. rev' den'd,* 154 Fed. Cl. 149 (2021); *Tullio,* 2019 WL 7580149, at * 14 (observing that "[t]he BLAST searches produced far too generalized information and the results did not match the immunologically relevant portions of the flu vaccine"), *mot. for review denied,* 149 Fed. Cl. 448 (2020); *A.T.,* 2021 WL 6495241, at *25 (finding that Dr. Steinman was not persuasive in his theory petitioner's HPV vaccination caused her narcolepsy in part because he did not "generat[e] reliable evidence of molecular mimicry via his BLAST searches"); *Mason v. Sec'y of Health & Human Servs.,* No. 17-1383V, 2022 WL 600415, at *27 (Fed. Cl. Spec. Mstr. Feb. 4, 2022) (finding that Dr. Steinman's BLAST search identifying homologies between the flu vaccine and several proteins was "only plausible"); *Schilling v. Sec'y of Health & Human Servs.,* No. 16-527V, 2022 WL 1101597, at *19 (Fed. Cl. Spec. Mstr. Mar. 17, 2022) (finding that discussion of Dr. Steinman's BLAST searches by the experts was not helpful to determining causation because "the potentiality of molecular mimicry *alone* is not enough to preponderantly establish causation" and the circumstances of this case made a homology determination irrelevant); *Caredio,* 2021 WL 4100294, at *31 (finding "that invocation of molecular mimicry (and a showing of homology as part of it) is insufficient to meet the 'can cause' prong"); *Montgomery v. Sec'y of Health & Human Servs.,* No. 15-1037V, 2019 WL 2511352, at *5 (Fed. Cl. Spec. Mstr. May 21, 2019) (finding that "BLAST searches do not provide any insight into cross reactivity" and "do little to substantiate Dr. Steinman's theory").

chance (Ex. K, p. 4-5; Ex. DD, p. 1-2). In his third report, Dr. Steinman remarks that it is "stunning" and "remarkable" that he located homologies relative to both of the vaccines at issue in this case. (Ex. 48, p. 10.) However, respondent's experts explain that such chance homologies are not at all unusual. It is well established that homologies do occur by chance without having any disease-causing significance. For example, Dr. Romberg explained that the specific orexin and orexin receptor protein segments at issue are "ubiquitous in nature." (Ex. K, p. 5.) He conducted his own BLAST searches that found over 20,000 distinct microbial peptides that have greater homology to these orexin segments than the HPV proteins, including E. coli, Lactobacillus, Clostiridium, Staphlococcus, Trichophyton, S. Pneumoniae, Adenovirus, and Human Herpes Virus. (*Id.*) In fact, Dr. Steinman himself acknowledges that molecular mimics are "widespread" even among healthy individuals. (Ex. 9, p. 24.) Therefore, as noted above, demonstrating homology alone – which even under the best of circumstances is the most that a BLAST search can show – does not support a theory of molecular mimicry under *Althen* prong one.

In sum, even accepting that BLAST search results have the potential to uncover possible homologies, results generated using the lenient parameters employed by Dr. Steinman are not predictive of a causally relevant homology. Therefore, the evidentiary value of these search results is limited and turns on whether the other evidence of record likewise supports a causal relationship between the vaccination and the type of injury at issue. Effectively, BLAST results are probably better viewed as potentially enhancing an otherwise supported theory rather than being viable as a foundation for such a theory. Without more, BLAST search results do not meet petitioner's preponderant burden of proof under *Althen* prong one. The additional evidence petitioner has presented relative to each of the two vaccines at issue is therefore key. That evidence is addressed in turn below.

c. There is Not Preponderant Evidence the HPV Vaccine Can Cause Narcolepsy

To further support the relevance of his BLAST searches relative to the HPV vaccine, Dr. Steinman presents two other pieces of evidence. First, he presents a large epidemiologic study by Arnheim-Dahlstrom, et al., that he indicates shows "impressive" and "quite revealing" increased incidences of narcolepsy. (Ex. 9, p. 28 (citing Arnheim-Dahlstrom et al., *supra,* at Ex. 37).) Second, he cites a study by Latorre, et al., examining T cell recognition in narcolepsy patients. He indicates that this study demonstrates the homology he identified in his BLAST searches to be causally meaningful to narcolepsy. (Exs. 40, 48, 53 (citing Latorre et al., *supra,* at Ex. 42).) Ultimately, neither of these pieces of evidence reliably supports Dr. Steinman's theory of causation.

Importantly, Dr. Steinman acknowledges that the Arnheim-Dahlstrom study did not find a statistically significant incidence rate of narcolepsy following vaccination. (Ex. 9, p. 28.) Of course, petitioners are not obligated to come forward with epidemiologic evidence. *Andreu,* 569 F.3d at 1378. Therefore, the Arnheim-Dahlstrom study is not

dispositive as evidence weighing against petitioner's theory. In fact, I have previously held that a similarly equivocal finding was a reason not to accept an epidemiologic study as strong evidence refuting a petitioners' theory of causation. *Madigan v. Sec'y of Health & Human Servs.,* No. 14-1187V, 2021 WL 3046614, at *17 (Fed. Cl. Spec. Mstr. June 25, 2021). However, the Arnheim-Dahlstrom finding *does not support* petitioner's case as Dr. Steinman suggests.

In asserting that this finding supports his opinion despite a lack of statistical significance, Dr. Steinman indicates that "to my knowledge, although I am a medical scientist and not a lawyer, statistical significance is a different standard than evidence supporting a 'preponderance of evidence' standard." (Ex. 9, p. 28.) Dr. Steinman asserts that, given the overall size of the study, the difference between the vaccinated and control groups is "impressive." (*Id*.) For purposes of his report in this case, Dr. Steinman indicates that "I do not apply the standard of 0.05 in order to form my opinion by 'preponderance of evidence.' This is a different standard than one that I might apply as a medical scientist in other contexts."[14] (*Id*.)

The Arheim-Dahlstrom study found 43 cases of narcolepsy in the control group occurring over the course of 2,374,402 person years, which they calculated to be an incidence rate of 1.81. (Arnheim-Dahlstrom et al., *supra,* at Ex. 37, p. 8.) Examining the vaccinated population, they found 6 cases of narcolepsy occurring over 230,013 person hours, which was an incidence rate of 2.61. (*Id.*) This difference between an incidence rate of 1.81 and 2.61 is the finding Dr. Steinman characterizes as "impressive" and "quite revealing." (Ex. 9, p. 28.) However, the 95% confidence intervals accompanying the findings indicate that the authors believe the true incidence rate for the control group may be as high as 2.44 and the true incidence rate for the vaccinated group may be as low as 1.17. (Arheim-Dahlstrom et al., *supra,* at Ex. 37, p. 8.) Thus, this is not simply a question of characterizing the size of an increase in the incidence rate as Dr. Steinman implies. It implicates whether the increase actually exists *at all* given the limitations of the available data.

Theoretically, an expert could present a reasoned disagreement with the statistical analysis in a study. However, Dr. Steinman has not done this. Discarding the commonly used 95% confidence interval in favor of simply deeming the finding subjectively "impressive" is not sound and reliable. In his second report, Dr. Steinman

[14] I must note that, separate and apart from the particular study at issue, Dr. Steinman's explicit reliance on the preponderant standard in itself reduces his credibility as an expert. It is, of course, true that petitioners in his program bear only a preponderant burden of proof. They are not obligated to prove their case with scientific certainty or by using epidemiology. Dr. Steinman cannot be faulted for merely being aware of that fact. However, these are considerations for the finder of fact when reviewing the record as a whole. Dr. Steinman's opinion is not meant to conduct that kind of weighing of the record using the preponderant standard because it is itself a part of the evidence subject to that review. The foundation of Dr. Steinman's opinion as an expert must be "sound and reliable" scientific explanation whereas opinions that state merely plausible or possible theories do not support petitioner's burden of proof. *Andreu,* 569 F.3d at 1378-79. By invoking the preponderant standard for his own review and interpretation of the scientific evidence, Dr. Steinman does not merely acknowledge the realities of this program, he crosses a line into effectively admitting that he has deliberately diluted the foundation for his opinion.

further stresses that the lack of clear associational evidence from the Arheim-Dahlstrom study cannot tell us what is happening with the one specific patient (petitioner) at hand. (Ex. 40, p. 2.) This is correct as far as it goes and is reflected in petitioner's burden of proof, which as noted above does not require her to prove her case epidemiologically. However, that is separate point that still does not permit Dr. Steinman to present a study that is neutral at best into evidence positively supporting petitioner's claim.

The only other piece of evidence presented in favor of a causal relationship between the HPV vaccine and narcolepsy is the Latorre study. At first blush, this study does appear to bolster petitioner's claim. In fact, this article has been viewed as significant evidence favoring vaccine causation in other narcolepsy cases. *Cobb,* 2023 WL 6457568, at *19-20; *Henkel,* 2022 WL 16557979, at *39-40; *but see A.T.,* 2021 WL 6495241, at *24-25. And, indeed, respondent's experts acknowledged that the Latorre study does significantly strengthen the autoimmune hypothesis for narcolepsy. (Ex. Z, p. 1.) Importantly, however, the Latorre study did not directly address whether the HPV vaccine causes narcolepsy. (Latorre et al., *supra,* at Ex. 42.) Apart from strengthening the autoimmune hypothesis more broadly, Latorre, et al., has the potential to link petitioner's HPV vaccine to narcolepsy solely because the study identified certain amino acid sequences as being reactive to CD8+ T cells, which could be consistent with the amino acid sequence homology Dr. Steinman identified in his BLAST searches. (Ex. 48 (citing Latorre et al., *supra,* at Ex. 42.) However, on closer inspection, Latorre, et al., does not support Dr. Steinman's theory.

Specifically, a diagram in Latorre maps two HCRT-specific CD8+ T-cell epitopes. The epitopes "were identified by screening the CD8+ T cell clones against overlapping peptides that span the entire length of HCRT." (Latorre et al., *supra,* at Ex. 42, p. 5 (fig. 4(d).) These two epitope sequences are: MGRRAGAEPAPRPCLGRRCS and PAPRPCLGRRCSAPAAASVA. (*Id*.) When Dr. Steinman first introduced the Latorre findings, he explained that the sequence RAGAEPAPRP had been identified by his BLAST search as containing a 5 of 10 amino acid match to the HPV vaccine. (Ex. 40, p. 5.) This same sequence is included in the first of these two Latorre sequences - MGR**RAGAEPAPRP**CLGRRCS. (Latorre et al., *supra,* at Ex. 42, p. 5 (fig. 4(d).) Thus, he indicated that the epitope sequences identified by Latorre as being recognized in narcolepsy by the CD8+ T cells confirmed that the homology he uncovered using BLAST is likely to be disease causing. (Ex. 40, p. 5.)

In response, however, Dr. Romberg presented a chart comparing the two recognized epitopes from the Latorre study with two additional epitopes the authors found were not recognized. This chart is as follows:

Peptide #	Peptide sequence	T-cell recognition?
1	NHAAGILTMGRRAGAEPAPR	not recognized
2	MGRRAGAEPAPRPCLGRRCS	recognized
3	PAPRPCLGRRCSAPAAASVA	recognized
4	LGRRCSAPAAASVAPGGQS(	not recognized

(Ex. Y, p. 2.) Because there is a sequence that is uniquely shared by the two recognized epitopes (PAPRCLGRRCS) that is not coextensive with the sequence Dr. Steinman produced using BLAST, and because the sequence identified by Dr. Steinman is also shared in substantial part with a sequence contained in an unrecognized epitope (peptide #1), Dr. Romberg opines that the more natural reading of the study results is that the sequence identified by Dr. Steinman as being shared with the HPV vaccine is not the amino acid sequence that Latorre et al. showed to be recognized by the T cells. (*Id*. at 2-4; *see also* Ex. DD, p. 3-4.) Further, Dr. Romberg completed his own BLAST search using the PAPRCLGRRCS sequence identified by Latorre et al. and confirmed that it included no match to the HPV vaccine proteins. (Ex. Y, pp. 2-4; Ex. DD, pp. 3-4.)

In response to Dr. Romberg, Dr. Steinman contends that Dr. Romberg's observation is not dispositive, because his animal model studies showed that truncation of one proline[15] can change which T cell clones are stimulated, suggesting that a single proline can be recognized by one clone and not another. (Ex. 48, pp. 2-3.) Thus, he contends that Dr. Romberg's table "does not inform us of whether or not RAGAEPAPRP would stimulate the clone found in the CSF of a narcolepsy patient because the overlapping 20-mer peptides does not include the identified sequence RAGAEPAPR**P**! The terminal **P** is intentionally **bold**, to show that Dr. Romberg's Table 1 lacks this." (*Id*. at 3 (emphasis original).) Dr. Steinman further stated: "To summarize, when the terminal P is present in RAGAEPAPRP, then the CD8 T cells are stimulated in patients with narcolepsy." (*Id*.)

Dr. Steinman's response is speculative and, even if credited, would not fully rebut Dr. Romberg's explanation of the Latorre et al. study. Even if a change in a single proline can result in different T cell recognition, nothing on this record apart from Dr. Steinman's *ipse dixit* supports that this actually explains the Latorre et al. findings. In making this point, Dr. Steinman effectively concedes that the Latorre et al. findings themselves do not readily support his theory as is. While Dr. Steinman may theoretically be correct that the single terminal "P" he has identified could explain why "RAGAEPAPR" was not recognized in peptide #1, his further assertion that we therefore know that "RAGAEPR**P"** does stimulate CD8 T cells does not necessarily follow. Instead, he was correct when he stated that the data identified by Dr. Romberg means we do not know "whether or not RAGAEPAPRP would stimulate the clone found in the CSF of a narcolepsy patient." (Ex. 48, p. 3.) But in any event, even if the non-recognition of peptide #1 does not *rule out* RAGAEPARP as causally meaningful, Dr. Steinman still has not addressed Dr. Romberg's assertion that the Latorre et al. findings *better support* PAPRCLGRRCS as the causally meaningful sequence. Thus, Dr. Romberg is persuasive in suggesting that Dr. Steinman's interpretation of the study findings is "unusual" and suggestive of confirmation bias. (Ex. DD, p. 4.) Finally, Dr. Romberg also notes that Dr. Steinman's focus on the P proline is in tension with his own

[15] A "proline" is "a nonessential amino acid." *Proline,* DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=41179&searchterm=proline (last visited May 7, 2024).

previously stated parameters for a causally meaningful homology (5 of 12 or 4 of 11 amino acids). (*Id.* at 3.)

In sum, petitioner's theory of causation seeking to implicate the HPV vaccine as a cause of narcolepsy relies on three points beyond the underlying autoimmune nature of the condition: (1) Dr. Steinman's BLAST search results showing short sequence homologies between vaccine components and orexin; (2) a single epidemiologic study by Arheim-Dahlstrom; and (3) a study by Latorre et al, that identified two peptide sequences recognized by T cells among narcolepsy patients. However, for the reasons discussed above, Dr. Steinman's homology is not in itself predictive of disease. The epidemiologic study did not conclude that the HPV vaccine was associated with narcolepsy. And the Latorre et al. study demonstrated that T cells in narcolepsy patients react to a peptide sequence different than the one Dr. Steinman had identified as a homology between the HPV vaccine and orexin. This does not preponderantly support a sound and reliable theory of causation under *Althen* prong one.

d. There is Not Preponderant Evidence the Seasonal Flu Vaccine Can Cause Narcolepsy

Initially, Dr. Steinman did focus on the HPV vaccine. (Exs. 9, 40.) It was not until his third report that Dr. Steinman indicated that a revised BLAST search uncovered homology between orexin and proteins in the influenza B component of the FluMist vaccine. (Ex. 48.) He explained that he located a 5 of 10 amino acid sequence "GAEPAPRPCL" as the "one and only" alignment between the FluMist components and orexin. (*Id*. at 8.) As with the sequence he identified for the HPV vaccine, he asserts that this sequence is likewise included in one of the two recognized peptides in the Latorre et al. study. (*Id.*) Specifically: MGRA**GAEPAPRCL**GRRCS. (*Id.*) However, the exact same issues as identified by Dr. Romberg exist for this sequence as exist for RAGAEPAPRP. That is, substantial portions of the sequence GAEPAPRPCL also overlap with peptide #1, which was not recognized by the T cells, and, in any event, PAPRPCLGRRCS, which is not coextensive with the sequence Dr. Steinman has identified, appears to be the more likely meaningful sequence within the Latorre et al. findings. Dr. Steinman has not addressed this issue at all vis-à-vis this particular sequence.

Apart from his reliance on the Latorre et al. study, Dr. Steinman has not otherwise demonstrated how the GAEPAPRCL sequence is causally meaningful nor that the FluMist vaccine can otherwise be implicated as a cause of narcolepsy. Dr. Steinman did cite his own prior work in Ahmed, et al., as supporting hypocretin receptor 2 as a pathway to autoimmunity in narcolepsy. (Ex. 9, p. 8 (discussing Ahmed et al., *supra,* at Ex. 25); Ex. 40, p. 6.) However, this study is explicit in concluding that different flu vaccines have different propensities to cause disease. Ahmed et al. did not include the FluMist vaccine and examined sequences other than what Dr. Steinman has identified as relevant from the FluMist vaccine. (Ahmed et al., *supra,* at Ex. 25.) For a more detailed discussion of the several papers Dr. Steinman has cited on this point (Ahmed, et al., *supra,* at Ex. 25; Tanaka, et al., *supra,* at Ex. 27; and Giannoccaro, et

al., *supra,* at Ex. 28), see *A.T.*, 2021 WL 6495241, at *19-25. In *A.T.*, I concluded that the disease-causing role of HCRT-R2 antibodies was not preponderantly established by these papers. (*Id.*) Additionally important in this case, however, Dr. Steinman has stressed that Ahmed, et al., implicates "hypocretin receptor 2 *and not* hypocretin." (Ex. 40, p. 6 (emphasis added).) Thus, it is not readily apparent, and Dr. Steinman has not otherwise explained, how his reliance on Ahmed, et al., squares with his emphasis on Latorre, et al., which appears to focus on hypocretin.

Although there are epidemiologic studies that suggest a relationship between the Pandemrix H1N1 pandemic flu vaccine and narcolepsy (Partinen, *supra,* at Ex. 38; Winstone, *supra,* at Ex. 39; Montplaisir et al., *supra,* at Ex. 52; Mignot, *supra,* at Ex. G), respondent's experts opined that, especially due to its AS03 adjuvant, which is not widely used among other flu vaccines, data pertaining to the Pandemrix vaccine is not relevant to other flu vaccines. (Ex. A, p. 5 (citing Duffy et al., *supra,* at Ex. I).) Although Dr. Steinman offered some criticisms of the epidemiology purporting to show that other flu vaccines are *not* associated with narcolepsy (Ex. 48, p. 11), he never challenged the causal significance of the AS03 adjuvant and never himself purported to rely on data pertaining to the H1N1 vaccine to support his theory. In fact, Dr. Steinman confirmed in both of his first two reports that he did not identify any relevant homology between orexin and the H1N1 component of the FluMist vaccine. (Ex. 9, p. 22; Ex. 40, p. 5.) He further acknowledged that the Latorre et al. study explicitly concluded that study's data did not implicate the H1N1 influenza vaccine as a cause of narcolepsy. (Ex. 40, pp. 5-6 (discussing Latorre et al., *supra,* at Ex. 42).) Accordingly, there can be no argument that data pertaining to the Pandemrix vaccine supports petitioner's claim.

In sum, as with the HPV vaccine, Dr. Steinman's BLAST search finding homology between the FluMist vaccine and orexin is entirely uncorroborated by any other evidence that suggests the FluMist vaccine can cause narcolepsy. For all the reasons discussed above, Dr. Steinman's proposed homology standing alone does not meet petitioner's preponderant burden of proof.

VI. Conclusion

Petitioner has suffered and for that she has my sympathy. Nothing in this decision is intended to minimize the impact her condition has had on her life. However, for all the reasons discussed above, petitioner has not demonstrated by preponderant evidence that her condition was caused by either of her vaccinations. Accordingly, this case is dismissed.[16]

IT IS SO ORDERED.

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

[16] In the absence of a timely-filed motion for review of this Decision, the Clerk of the Court shall enter judgment accordingly.