In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

No. 17-168V

(to be published)

* *	Chief Special Master Corcoran
PATRICK HOCK, *	
*	
Petitioner, *	Filed: September 30, 2020
*	
v. *	Entitlement; flu vaccine; rheumatoid arthritis; epidemiology
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SECRETARY OF HEALTH *	
AND HUMAN SERVICES, *	
*	
Respondent. *	
*	
* *	

Amy Senerth, Muller Brazil, LLP, Philadelphia, PA, for Petitioner.

Dhairya Jani, U.S. Dep't of Justice, Washington, D.C., for Respondent.

DECISION DENYING ENTITLEMENT[1]

On February 3, 2017, Patrick Hock filed a petition seeking compensation under the National Vaccine Injury Compensation Program ("Vaccine Program").[2] Petitioner alleges that he developed polyarthritis/rheumatoid arthritis ("RA") as a result of receiving the seasonal influenza ("flu") vaccine on October 20, 2015. Petition at 1 (ECF No. 1).

A hearing in this matter was held on March 12, 2020. ECF No. 64. After consideration of the filings in this case, I deny entitlement. As set forth in greater detail below, Petitioner's causation theory includes several components that are based on sound science. But the *overall* theory is not itself sufficiently reliable to link those components into something that preponderantly establishes ("more likely than not") that the flu vaccine can initiate or trigger

[1] This Decision will be posted on the Court of Federal Claims' website in accordance with the E-Government Act of 2002, 44 U.S.C. § 3501 (2012)). **This means that the Decision will be available to anyone with access to the internet.** As provided by 42 U.S.C. § 300aa-12(d)(4)(B), however, the parties may object to the Decision's inclusion of certain kinds of confidential information. Specifically, under Vaccine Rule 18(b), each party has fourteen days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, the whole Decision will be available to the public. *Id*.

[2] The Vaccine Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3758, codified as amended at 42 U.S.C. §§ 300aa-10 through 34 (2012) [hereinafter "Vaccine Act" or "the Act"]. Individual section references hereafter will be to § 300aa of the Act (but will omit that statutory prefix).

seropositive RA of the kind diagnosed in Mr. Hock. At most, preponderant evidence supports the conclusion that Petitioner experienced an immediate, transient reaction to the vaccine that included symptoms that were arthritis-like in presentation but soon resolved, and thus did not constitute the actual beginning of his subsequently-diagnosed RA. Indeed – the parties' experts agree that Petitioner's RA disease process had already begun *before* he received the flu vaccine at issue in this case, and it has not been preponderantly shown that the vaccine contributed to that process.

I. *Factual Background*

On October 20, 2015, Mr. Hock (who was then 52 years old) received a flu vaccine[3] at a Walgreens in Port Orchard, Washington. Ex. 1 at 2; Ex. 7 at 1-3. At the time he was generally in good health, with no objective prior history of arthritis. However, Petitioner did have a family history of RA, and had experienced a number of issues relating to the spine and the ulnar nerve in the elbow. Ex. 2 at 9, 11, 15, 205; Ex. 3 at 17, 19, 109, 296, 314; Ex. 6 at 23. He also had a history of being a smoker (reporting he previously used 20 packs of cigarettes per year)[4], although he purportedly stopped smoking in 2010. Ex. 2 at 11; Tr. at 152.

Four days later (October 24, 2015), Petitioner presented to Harrison Medical Center Emergency Department with a chief complaint of severe ankle and joint pain, left knee pain, and pain in his wrist (which he later reported had manifested at the time he was admitted to the hospital). Ex. 2 at 9, 14, 16. He described a course of symptoms that began as "discomfort" in his left knee, leading to more severe pain in his right ankle and then the other mentioned joints. *Id.* at 9. Petitioner's right ankle pain was severe enough to make walking difficult, but he displayed no joint swelling, with the right ankle only appearing mildly red. *Id.* at 9, 11, 12. He also specifically reported that he had recently received the flu vaccine. *Id.* at 9.

Mr. Hock was admitted to the hospital based upon an initial treater assessment of "probable cellulitis" in his right ankle. Ex. 2 at 14. He displayed no fluid in the joints he complained of, and so it was proposed that he undergo a right ankle joint aspiration[5] to attempt to ascertain the cause of his pain. *Id.* His recent flu vaccine was also proposed as possibly "contributory" to his complaints. *Id.* After admission, Petitioner received the aspiration, which revealed no crystals

[3] Mr. Hock specifically received Fluvirin, an inactivated, trivalent, nonadjuvanted vaccine primarily aimed at immunizing a person against the influenza A and B wild virus strains. Ex. 1 at 2; *Package Insert - Fluviron*, U.S. Food and Drug Administration: Vaccines, Blood & Biologic, https://www.fda.gov/vaccines-blood-biologics/vaccines/fluvirin (last visited Sept. 30, 2020).

[4] A record from Petitioner's October 30, 2015 ER visit, however, includes the representation (taken in Petitioner's medical history – and hence presumably from him) that prior to quitting he smoked 1.5 packs of cigarettes a day, which would be a far larger number on a yearly basis. Ex. 2 at 202.

[5] Aspiration (withdrawal of the fluid) may be performed on any major joint. Arthrocentesis (fluid analysis) is then performed to establish the diagnosis of joint infection, arthritis, crystal-induced arthritis (gout and pseudogout), synovitis, or neoplasms involving the joint. The procedure is also used to identify the cause of joint inflammation or effusion. *Mosby's Manual of Diagnostic and Laboratory Tests* 577 (6th ed. 2018).

(precipitates in the synovial fluid that suggest the presence of gout)[6] and produced negative fluid cultures (thus casting doubt on the conclusion that the pain was infectious in origin). *Id*. at 16. He also continued to display no swelling or joint effusion/fluid. *Id*. at 24. Mr. Hock now informed treaters that his symptoms began about a day after his vaccination (or on October 21, 2015). *Id*.

In the course of hospitalization, a treater proposed that Petitioner was experiencing some kind of polyarthralgia or polyarthritis. Ex. 2 at 27. The differential diagnosis for explaining the source of this polyarthritis/polyarthralgia included a virus, autoimmune disease (including RA), or "immune reaction to influenza vaccination." Ex. 2 at 27. After the inconclusive joint aspiration, the differential largely remained the same, and continued to include a reaction to the vaccine as possibly explanatory. *Id.* at 34.

Petitioner was discharged October 26, 2015. Ex. 2 at 16. The discharge diagnosis focused on polyarthritis/polyarthralgia, but included the discharge physician's view that Petitioner had likely experienced "serum sickness"[7] relating to the recent vaccination, although this treater did not propose or articulate how this had developed into his polyarthritis symptoms, or whether it explained them entirely. *Id.* Mr. Hock was advised to follow up with his primary care physician if his symptoms persisted or worsened. *Id.*

Four days later, on October 30, 2015, Petitioner returned to Harrison Medical Center Emergency Department complaining of worsening joint pain, right ankle pain, and polyarthralgia, and was again admitted to the hospital. Ex. 2 at 198. Mr. Hock specifically reported a history consistent with what the records from his October 24th-26th hospitalization set forth, and added that his symptoms had recurred, and become intolerable, once he completed his steroid course. *Id.* But he denied any joint redness, drainage, or warmth. *Id*.

As before, examination revealed pain after movement of Petitioner's right ankle, plus shoulder and wrist and some ankle swelling (although it was deemed minimal). Ex. 2 at 202. Mr. Hock was briefly hospitalized again until October 30, 2015, diagnosed with polyarthralgia and polyarthritis of multiple sites, and prescribed medication, including a corticosteroid. *Id.* at 198-204, 214-19. It was also proposed (consistent to treater initial opinions) that Mr. Hock's symptoms were attributable to an "auto -immune reaction" to the flu vaccine, manifesting as serum sickness-related symptoms, although RA was also included in the differential. *Id.* at 204.

After discharge, Mr. Hock saw a nurse-practitioner in early November for review of his ongoing joint pain and weakness, and was referred for a rheumatology consult. Ex. 3 at 280-84. A

[6] Gout is a group of disorders of purine metabolism, manifested by various combinations of (1) hyperuricemia and uric acid calculi; (2) recurrent acute inflammatory arthritis induced by crystals of monosodium urate monohydrate; and (3) tophaceous deposits of these crystals in and around the joints of the extremities, sometimes causing crippling destruction of the joints. *Dorland's Illustrated Medical Dictionary* 790 (33rd ed. 2020) (hereinafter, "*Dorland's*").

[7] Serum sickness in association with vaccination can manifest with symptoms such as joint pain, edema, and fever. *Dorland's* at 1678.

month passed before Mr. Hock saw another medical treater. On December 10, 2015, Petitioner had an appointment with Dr. Marat Gadzhiev, a rheumatologist, for "workup of possible inflammatory arthritis." *Id.* at 270. Mr. Hock repeated his prior history of onset of symptoms, beginning with left knee pain progressing to his ankles, a few days after vaccination that October. Ex. 3 at 266. He now reported chronic pain in his left foot and wrist, but added that he had not experienced a recurrence of acute joint pain. *Id.*

Dr. Gadzhiev reviewed Petitioner's prior testing results, noting that the ankle aspiration had not revealed anything significant. Ex. 3 at 266. Examination revealed no joint tenderness or swelling (clinical indicia of RA), along with full joint range of motion. *Id.* at 269. Mr. Hock's symptoms were also not deemed consistent with a psoriatic arthritis, despite the fact that he had some prior history of psoriasis. *Id.* at 270. But testing revealed a slightly elevated rheumatoid factor, a biomarker strongly associated with RA. Ex. 3 at 269.

Consistent with prior treaters, Dr. Gadzhiev opined that Petitioner had likely suffered a severe reaction to the flu shot, leading to "an acute onset of reactive arthritis," but that it appeared his initial symptoms had "now completely resolved." Ex. 3 at 270. But Dr. Gadzhiev expressed the concern that Petitioner's family history of RA, coupled with his lab results, could mean that he was himself in the initial stages of developing true RA. *Id.* at 270. To explore that possibility, Dr. Gadzhiev ordered some additional lab testing for Petitioner, including tests to look for the presence of anti–cyclic citrullinated peptide ("anti-CCP") antibodies (another biomarker associated with RA),[8] as well as other signs of inflammation. *Id*. The testing revealed high levels of the anti-CCP antibodies, causing one of Dr. Gadzhiev's colleagues to deem Petitioner's risk of developing inflammatory arthritis to be "quite high." *Id.* at 265. Radiologic imaging of Mr. Hock's hands, however, revealed none of the features associated with inflammatory arthropathy. *Id.* at 241-32. Petitioner was prescribed Methotrexate, an anti-rheumatic drug widely used to treat RA, and was asked to follow up with Dr. Gadzhiev in 2016. *Id.* at 110**,** 265.

Mr. Hock thereafter continued to experience symptoms reflecting joint pain. On December 31, 2015, for example, Petitioner returned again to the emergency room with complaints of severe left ankle pain and swelling, and was re-admitted to the hospital thereafter for several days. Ex. 3 at 60, 100-06; 410-11. His diagnoses included seropositive RA and cellulitis. Ex. 3 at 60. Petitioner was discharged on January 3, 2016, and prescribed antibiotics to treat a suspected cellulitis-related infection[9] while being told to suspend medications he had been taking to treat RA and related symptoms until the antibiotics course was completed. *Id.* at 71-74, 252; Ex. 4 at 60-65.

Petitioner was monitored throughout 2016 by Dr. Gadzhiev for his suspected RA. *See,* e.g., Ex. 3 at 54-59, 67, 119-25, 183-89; Ex. 4 at 240-30, 101-105. He continued to complain of ongoing polyarthritis symptoms, including ankle pain worsened by walking. Ex. 3 at 67-74, 93-98. The most recent contemporary records filed in this case (from 2017) establish that Petitioner still

[8] Ex. 3 at 270.

[9] Mr. Hock was prescribed an antibiotic for the suspected cellulitis. Ex. 3 at 60.

experiences joint pain in his knees, ankles, elbows, and wrists, plus morning stiffness. Ex. 6 at 25. Mr. Hock remains diagnosed with seropositive RA, and has kept taking Methotrexate. *Id.* at 25, 29.

II. *Testimony at Hearing*

A. Dr. Paul J. Utz

Dr. Utz, an immunologist and rheumatologist, testified at hearing for Petitioner, and also submitted a total of three written reports. Tr. at 5-85; Report, dated Apr. 1, 2018, filed as Ex. 8 (ECF No. 26) ("First Utz Rep."); Report, dated Dec. 13, 2018, filed as Ex. 9 (ECF No. 30-1) ("Second Utz Rep."); Report, dated Aug. 7, 2019, filed as Ex. 10 (ECF No. 39-2) ("Third Utz Rep."). Dr. Utz generally opined that the flu vaccine could invoke RA through the mechanism of molecular mimicry, and did so herein to Petitioner.

Dr. Utz graduated from Stanford University Medical School in 1991. *See* CV, filed as Ex. 11 (ECF No. 61), at 1. He was board certified in internal medicine from 1994 to 2004, and in rheumatology from 1996 to either 2016 or 2017, but has not had the time recently to take the tests necessary for recertification. Tr. at 8. He is a professor of medicine at Stanford University, and has served as Acting Chief of the University of Medicine's Division of Immunology and Rheumatology, and as Director of the Center for Clinical Immunology. Ex. 11 at 1, 2. Dr. Utz has authored numerous articles and publications, some of which address RA and its causes, and has direct familiarity working on vaccine development for the National Institutes of Health. *Id.* at 6; Tr. at 7, 9. Dr. Utz currently runs a research laboratory that studies autoimmune diseases in humans. Ex. 11 at 6; Tr. at 7. Most of his time is today devoted to research or administrative matters at Stanford's medical school, although he sees patients at a Palo Alto VA hospital. Tr. at 7-8. He has, however, treated many RA patients. *Id.* at 9-10.

Dr. Utz began his testimony with an overview of RA. He deemed it the most common of rheumatologic diseases, affecting one percent of the population. Tr. at 13. RA involves a "break in tolerance to self" – meaning that it is autoimmune in nature – and results in painful arthritic inflammation in the hand and wrist joints most typically. *Id.* The anti-CCP antibody is considered to be "directly pathogenic" in RA, and has even in experiments been shown to have the capacity to accelerate the disease process. *Id.* at 75. This autoantibody causes harm by directly cross-reacting with self-antigens in collagen found in the joints, damaging the joints in the process. *Id.* at 76.

"Seropositive" RA involves the classic clinical symptoms of arthritis, in the presence of a positive rheumatoid factor or high levels of anti-CCP antibodies (which are found in 60 to 70 percent of all RA patients). Tr. at 16-17, 18-19. Seronegative RA occurs in 20 to 30 percent of RA patients, and does not feature such positive antibody tests. *Id.* at 19. There are also noninflammatory arthritic conditions and diseases, although they would not include RA. *Id.* And

regardless of its form, RA can present clinically in different ways, and frequently does so "insidiously," with a slow and gradual onset of increasing stiffness and swelling over time – but can also appear "explosively" as well. *Id.* at 19-20.

It cannot be said with certainty what is the cause of any person's RA – or what would trigger the anti-CCP antibodies usually responsible for causing harm in seropositive RA (although Dr. Utz allowed that the increase of these autoantibodies in a person over time eventually likely reaches a threshold level sufficient to cause injury). Tr. at 76-77. However, Dr. Utz noted that certain risk factors exist that make some individuals more susceptible to RA. *Id*. at 52-53. Women (who already make of the majority of individuals suffering from autoimmune conditions) are particularly susceptible, as are smokers (a group that Dr. Utz admitted included Mr. Hock until 2010, and which he deemed a significant risk factor in evaluation of Petitioner's illness). *Id.* at 17, 42. People can have a family history of RA (another risk factor relevant to Petitioner). *Id.* at 18. Certain genetic markers are also associated with the presence of RA. Some of these are strongly linked to the existence of anti-CCP antibodies (since these antibodies occur in part as the result of genetic error),w which in turn are also associated with smoking. *Id.* at 18.

Mr. Hock carried such genetic risk factors, in particular because he had tested positive for high levels of these anti-CCP antibodies. Tr. at 18. It was also highly likely, Dr. Utz admitted, that Petitioner possessed these anti-CCP antibodies *before* his vaccination. Tr. at 25. The presence of such antibodies, however, did not in Dr. Utz' view guarantee that an individual would develop RA – any more than any risk factors predicted RA's occurrence. Tr. at 24-25, 42. Nor were they necessarily suggestive that a person could properly be diagnosed (as Dr. Oddis proposed) as having "preclinical RA," since it could not be predicted that mere possession of the anti-CCP antibodies would later lead to RA. *Id.* at 26.[10]

Dr. Utz discussed the role vaccines in general, and the flu vaccine in particular, likely played in Petitioner's disease process leading to RA. All vaccines, he maintained, must ultimately activate the adaptive immune system to be effective. Tr. at 31.[11] This is because the production of antibodies that will respond to future infection can only occur with an "active B cell response," which occurs during the adaptive, secondary immune response. *Id.* T cells, which directly attack pathogens (rather than manufacture antibodies to perform this function, as B cells do), are also integral to the adaptive response, as the "right" T cells should be trained to respond to specific antigens. *Id.* at 38-39. But Dr. Utz admitted that much less is known about how T cells "learn" to attack certain infectious antigens. *Id.*

[10] In fact, Dr. Utz maintained that research he had performed or contributed to had observed that even seronegative RA patients often possessed some anti-CCP antibodies, or other antibodies likely to cross-react against collagen, even if those levels were not sufficient to be identified by standard lab tests. Tr. at 48-49.

[11] Dr. Utz later noted, however, that he did not mean to propose that the immune system is "generally" activated by vaccination, clarifying (with specific reference to literature filed in connection with his report) that he maintained instead that a specific subset of genes specific to males are stimulated by certain cytokines (the production of which is itself vaccine-instigated), thus encouraging a faster innate response in men when exposed again to the same vaccine antigen. Tr. at 59; Second Utz Report, at 10.

In an aberrant adaptive immune response, "something in the vaccine" triggers a pathogenic process in B and T cells – but the triggering begins with the immediate innate response, when proinflammatory cytokines are secreted upon vaccine introduction. Tr. at 32. The innate part of the pathologic cycle is understood to be mediated by cytokines - immune system hormones "that get secreted very rapidly as part of an immune response." *Id.* at 30. Proinflammatory cytokines responding to vaccination have the capacity to cause fever or inflammation. *Id.* This innate response is rapid, especially in men. *Id.* at 30-31. In this case, Dr. Utz maintained that the initial innate response to the vaccine was evidenced by Petitioner's knee pain symptoms within 24 hours of vaccination. *Id.* at 32.

The second "leg" of the immune response elicited by the flu vaccine, according to Dr. Utz's theory, involves the "bystander activation" of autoreactive T cells. As Dr. Utz explained, individuals possess autoreactive T cells capable of recognizing "tens of thousands" of other peptides – and are thus potentially cross-reactive (if the recognized peptide is a mimic of a self amino acid sequence). Third Utz Rep. at 4. In addition, individuals susceptible to RA (as Mr. Hock likely was, given his history as well as the evidence that he possessed anti-CCP antibodies) already possess the necessary B cells that would be specific to the infectious antigens, as well as specific T cells that would respond (whether directly or by stimulating the specific B cells). Tr. at 32; Third Utz Rep. at 9. This response would progress negatively, with a steady increase in symptom severity as the innate reaction gave way to an adaptive response that could not stop once it begins. Tr. at 40-41. The "transition," so to speak, from an aberrant innate to adaptive response would thus be furthered by the pre-existing autoreactive B and T cells that are "ready to go." *Id.* at 79.

Dr. Utz maintained that some literature he had filed demonstrated that "T cells derived from RA patients can be stimulated by [flu vaccine antigens]," thus allowing for the conclusion that a bystander-generated cross-reaction was possible. Third Utz Rep. at 4 (citing M. Skinner et al., *Lymphocyte Responses to DR1/4 Restricted Peptides in Rheumatoid Arthritis* 54 Ann Rheum Dis 171 (1994), filed as Ex. 10.1 on August 7, 2019 (ECF No. 39-3); X. Li et al., 24 *Influenza Virus Haemagglutinin-Derived Peptides Inhibit T-cell Activation Induced by HLA-DR4/1 Specific Peptides in Rheumatoid Arthritis,* 24 Clinical and Experimental Rheumatol. 148-154 (2006), filed as Ex. 8.11 on August 7, 2019 (ECF No. 38-12) ("Li")). However, he went on to admit that he could *not* identify evidence directly demonstrating through experimentation that the flu vaccine antigen "can bind to and activate a collagen-specific T cell," although in so admitting he maintained that the experimentation required to substantiate the assertion would be highly complex. Third Utz Rep. at 4.

Finally, the adaptive stage of the overall immune response triggered by the receipt of the flu vaccine would also play a role in encouraging RA. The flu vaccine contains an antigen that was capable of directly causing an autoimmune cross-reaction, via the process of "molecular mimicry,"

and further contributing to the development of RA. Tr. at 3, 62-63.[12] Specifically, Dr. Utz noted that it contains hemagglutinin, "a protein that is expressed on the surface of the influenza virus," and is included as an antigen in order to "teach" the body to recognize it in the future, and in so doing produce pathogen-fighting antibodies that will attack a wild virus version. *Id.* at 35, 36. But hemagglutinin has also been demonstrated to share one or more epitopes (the part of a foreign antigen recognizable by the immune system) with self-peptides like collagen that are the known situs of RA's autoimmune attack[13] – making the two molecular mimics. *Id.* at 36-37, 63; First Utz Rep. at 17-23 (citing A. Dessen et al., *X-Ray Crystal Structure of HLA-DR4 (DRA *0101, DRB1 *0401 Complexed with a Peptide from Human Collagen II* 7 Immunity 473,-481 (1997), filed as Ex. 8.9 on August 7, 2019 (ECF No. 38-10)("Dessen"); J. Hennecke et al., *Structure of a Complex of the Human T Cell Receptor (TCR) HA1.7, Influenza Hemagglutinin Peptide, and Major Histocompatibility Complex Class II Molecule, HLA-DR4 (DRA *0101 and DRB1 *0401): Insight into TCR Cross-Restriction and Alloreactivity*, 195 J. Exp. Med. 571-581 (2002), filed as Ex. 8.10 on August 7, 2019 (ECF No. 38-11).

Dr. Utz specifically maintained that mimicry between the hemagglutinin in the vaccine and collagen has been demonstrated by the fact that the "DR4 molecule" (strongly associated with seropositive, high-anti-CCP antibody-level RA) interacts easily both with hemagglutinin peptides (chains of amino acids) and collagen – thus establishing the structural/sequential similarity between the two. Tr. at 36-37, 63-64. However, Dr. Utz admitted on cross-examination that Dessen's authors did *not* themselves conclude that there was in fact a molecular mimicry-driven cross-reaction between hemagglutinin on the surface of the influenza virus and collagen, such that the flu vaccine could be said to "cause" arthritis. *Id*. at 64; Dessen at 474-477. He made the same admission in his third report, walking back assertions about the association between hemagluttinin and the "immune response in RA" he had made in his prior reports regarding other items of literature (not discussed at hearing) that touched on this point. Third Utz Rep. at 2-3.

Based on this mimicry, Dr. Utz opined that the flu vaccine could "specifically activate[] the CCP-producing cells," releasing antibodies that cross-reacted with self structures and thus cause RA-associated symptoms. Tr. at 33. In addition, activated T cells specific for hemagglutinin (and thus collagen as well given the structural similarity) would themselves increase inflammation (through the release of proinflammatory cytokines), due to the same cross-reactive potential attributable to mimicry. *Id.* at 37-38. These activated T cells would target the collagen in joints, "and that's where they do their damage," in conjunction with the cross-reacting antibodies. *Id.* at 39-40. However, Dr. Utz acknowledged that (as stated in his first report) he could not conclusively show that the same flu vaccine component did in fact "directly influence" T cells specific to

[12] Dr. Utz later proposed that arguably a wild virus flu infection could accomplish the same, causing "joint discomfort" that could later lead to arthritis. Tr. at 78. He admitted, however, that he could identify no literature suggesting an association between the wild flu virus and arthritis. *Id.*

[13] Collagen itself, Dr. Utz testified, is well-understood by science to be a "bona fide antigen in RA" – both because it is the situs of autoimmune attack in the body leading to RA symptoms, and also because it has been experimentally shown to serve as a means of inducing a "rheumatoid arthritis-like disease" in animal subjects injected with collagen peptides. Tr. at 39.

collagen peptide (adding that although the research or experimentation required to do so would be complex, arguably some of it was accomplished in Li). *Id.* at 68-69; First Utz Rep. at 25.

To more specifically substantiate a link between the flu vaccine and RA, Dr. Utz referenced several items of literature. One review article described the ability of a bacterial protein, enolase, to break tolerance and to cause arthritis in an animal model, acting as a molecular mimic, thus offering a comparison to how a viral protein like influenza might accomplish the same. Tr. at 46 (citing C. Bingham, III et al., *Periodontal Disease and Rheumatoid Arthritis: The Evidence Accumulates for Complex Pathobiologic Interactions*, 25(3) Curr. Opin. Reheumatol. 345-353 (2013), filed as Ex. 8.5 on August 7, 2019 (ECF No. 38-6) ("Bingham"); K. Lundberg et al., *Periodontitis in RA – the Citrullinated Enolase Connection*, 6 Nat. Rev. Rheumatol. 727-730 (2010), filed as Ex. 8.6 on August 7, 2019 (ECF No. 38-7). He also offered some articles supporting his contention that the flu vaccine could rapidly activate inflammatory cytokines via the innate immune response, which in turn would progress into the molecular mimicry cross-reaction emblematic to an aberrant adaptive response. Third Utz Rep. at 9; Li at 153. He admitted, however, that he could find no epidemiologic support for an association between the flu vaccine and RA -- although he maintained that because of the variability in possible immune response between individuals, the absence of such evidence did not necessarily undercut his theory. Tr. at 48.

Turning to the facts of this case, Dr. Utz proposed that Mr. Hock was correctly diagnosed with seropositive RA. Tr. at 13, 19. In his view, Petitioner's circumstances could be shown to meet the classification criteria established by the "two main governing bodies" in the medical field of rheumatology – the American College of Rheumatology and the European League Against Rheumatism ("EULAR") – and although Dr. Utz agreed that these criteria were primarily designed so that epidemiologic studies would be uniform in their use of the classification of RA, they also had some diagnostic value. *Id.* at 13-14. Under the older version of the American College of Rheumatology criteria, an individual need meet only four of seven criteria to be deemed to have RA – and in Dr. Utz's reading of the record, Petitioner met five (he had experienced morning stiffness; had arthritis in three or more joint areas in the body; had symmetric/simultaneous involvement of same joint area on both sides of the body; had hand/wrist joint swelling; and was positive for rheumatoid factor as well as anti-CCP antibodies). Tr. at 15-16; First Utz Rep. at 7.

Petitioner also met six out of the ten EULAR criteria, since (in addition to the factors already described) he possessed elevated levels of inflammation biomarkers, although Dr. Utz only characterized Mr. Hock's rheumatoid factor levels as "low positive." Tr. at 16. Nevertheless, Dr. Utz characterized Petitioner's RA as "atypical," since it did not have a severe and consistent cast, although he also noted that its uncommon course and presentation ultimately corroborated why it might be vaccine-caused. *Id.* at 20, 50.

As of October 24, 2015, Mr. Hock went to the ER and was initially diagnosed with cellulitis, but Dr. Utz disputed the accuracy of the diagnosis, given that Petitioner went on over

time to display the symptoms or test results above to suggest RA was a more accurate descriptor. Tr. at 20-21. Dr. Utz did, however, agree that the evidence that Petitioner displayed arthritic symptoms in many of his joints made the discharge diagnosis of polyarthritis reasonable (although this further undercut cellulitis as explanatory, since that condition is limited to one location). *Id.* at 21. And then more evidence supporting the RA diagnosis came by the end of October, as Petitioner began to experience more widespread symptoms. *Id.* at 22. The increase in symptoms and severity over time were factors that suggested the accuracy of the diagnosis. *Id.* at 23.

These same facts, Dr. Utz maintained, cut against the contention of Respondent's expert, Dr. Oddis, that Mr. Hock only suffered from preclinical RA. Tr. at 49. Not only did Petitioner's circumstances satisfy the two most accepted classification criteria for RA, but he also was diagnosed with RA and treated with drugs commonly prescribed for it. *Id.* at 49-50. However, Dr. Utz readily conceded that Petitioner likely possessed the anti-CCP antibodies and other biomarkers relevant to RA prior to vaccination (along with Petitioner's purported autoreactive B and T cells). *Id.* at 75.

Dr. Utz further concluded that the flu vaccine Petitioner received was the most likely cause of his RA manifesting as it did. He saw no other possible explanation for an alternative trigger given the record. Tr. at 48-49. He acknowledged, however, that the flu vaccine was properly recommended for individuals with RA, since their immune systems were likely compromised, and thus at great risk for infection. *Id.* at 71. He also agreed that (consistent with the fact that Petitioner likely possessed certain RA-associated autoantibodies, like anti-CCP antibodies, prior to vaccination) the vaccine was not responsible for their generation (at least at the time of vaccination) – although (somewhat inconsistently) his theory goes on to rely on the conclusion that the vaccine would in fact play a role in stimulating the production of these autoantibodies later on. *Compare Id.* at 75 (flu vaccine not related to Petitioner's generation of RA autoantibodies) with *Id.* at 32-33 (cross-reaction of vaccine components "specifically activated the CCP-producing B cells").

Dr. Utz embraced a one-day onset as medically acceptable. Tr. at 27. He attributed this not to the effects of autoantibody cross-reactions brought about by the molecular mimicry that was central to his theory, however, but solely to the fast activation of the innate immune system caused by vaccination, leading to cytokine production. *Id.* In so maintaining, he took issue with the nascent treater views that Mr. Hock's symptoms were attributable to serum sickness, or were proof of a transient reactive arthritis that later resolved. *Id.* at 29-30. The release of these cytokines would be sufficient to cause joint pain symptoms right away.[14] Amplification of the initial response would occur as the vaccine antigens were transported to the draining lymph nodes, causing "bystander activation" of other immune cells. *Id.* at 42. Eventually, over a longer period of time the cross-reaction of B and T cells via molecular mimicry would occur, but secondarily, once the adaptive

[14] In discussing the harmful cytokine impact, Dr. Utz invoked the intense and harmful response to the coronavirus that many have experienced, noting that it can lead to an unstoppable "cytokine storm" producing acute inflammation. Tr. at 30.

immune reaction began to work. *Id.* at 28-29, 30, 42-43. The timeframe in which this occurred for Petitioner also mapped well against how long it would be expected medically for RA to progress as the adaptive system became active. *Id.* at 51.

Such a short timeframe between vaccination and onset was significant in Dr. Utz's view. Although Mr. Hock may have had several risk factors to develop RA (and likely possessed anti-CCP antibodies before his vaccination), he developed his symptoms within 24 hours post-vaccination, with little to no evidence of persistent or recurring polyarticular joint symptoms prior to then. This confirmed the role the flu vaccine likely played in triggering Petitioner's RA. Tr. at 25. Indeed, Dr. Utz opined that the lack of testing for the anti-CCP antibodies prior to vaccination underscored the fact that treaters did not suspect RA to be possible for Petitioner before he was vaccinated. *Id.* And Petitioner's subsequent course, which required the attention of a rheumatologist and medicinal treatments like Methotrexate, was fully consistent with RA. *Id.* at 26-27.

To support his timeframe contentions, Dr. Utz referenced several items of literature. Tr. at 43-44 (citing J. Tsang et al., *Global Analyses of Human Immune Variation Reveal Baseline Predictors of Postvaccination Responses* 157 Cell 499-513 (2014), filed as Ex. 8.15 on August 7, 2019 (ECF No. 38-16) ("Tsang"); L. Franco et al., *Integrative Genomic Analysis of the Human Immune Response to Influenza Vaccination,* 1 eLife 1-18 (2013), filed as Ex. 8.14 on August 7, 2019 (ECF No. 38-15) ("Franco"). Tseng and Franco, along with research Dr. Utz had been involved in, "demonstrated pretty unequivocally" that male reactions to vaccination are faster and more robust in subsequent exposures to the same vaccine, thus substantiating that the reaction could occur in as short a timeframe as experienced by Mr. Hock. Tr. at 44, 56-59.

Moreover, the pathologic nature of this faster effect would be increased in individuals who already had high levels of anti-CCP antibodies. In Tsang, immune parameters were analyzed in depth, both at baseline and in response to influenza vaccination. Tsang at 499. Transcriptional profiling of peripheral blood mononuclear cells revealed substantial changes on days one, three, and seven postvaccination, reflecting early innate immune activation. *Id.* at 500. In Franco, a longitudinal study combining genetic, transcriptional, and immunologic data in humans given seasonal influenza vaccine showed that variation at the level of genes involved in membrane trafficking and antigen processing significantly influences the human response to influenza vaccination. Franco at 1.

Another article established that the blood of RA patients would upregulate the same kind of proinflammatory cytokines after stimulation with hemagglutinin – thus corroborating the likelihood of a faster immune response in those susceptible to RA. Tr. at 59-60 (citing Li). And research regarding autoreactive T cells further bulwarked the contention that a short timeframe from vaccination to onset was reasonable. Tr. at 45 (citing O. Snir et al., *Identification and Functional Characterization of T Cells Reactive to Citrullinated Vimentin in HLA-DRB1 *0401-Positive Humanized mice and Rheumatoid Arthritis Patients*, 63 Artritis & Rheumatism 2873-

2883 (2011), filed as Ex. 10.3 on August 7, 2019 (ECF No. 39-5). Such T cells need not be specific to RA, or other infectious-borne or autoimmune illnesses, to be potentially harmful within an autoimmune process, but are in most cases suppressed by the immune system. Tr. at 45. Dr. Utz opined that Mr. Hock likely possessed these kind of damaging T cells. *Id.*

On cross, Dr. Utz admitted that none of the literature he had filed directly addressed whether the flu vaccine was itself associated with RA – let alone the wild flu virus - nor had he ever researched the issue personally. Tr. at 53-54, 78. He agreed that his opinion in this case was consistent with what he had offered in other Program cases (discussed below), in which he had also proposed that a predisposed individual with some unidentified immune system "defect" developed RA due to vaccination. *Id.* at 61-62.[15] A person like Mr. Hock likely possessed a "unique B and T cell repertoire" sufficient to make him at greater risk for an abnormal immune response. *Id.* at 65. But Dr. Utz also noted that other individuals suffering from RA whose illness he had opined in the past was likely vaccine-caused or associated would each present unique circumstances, even if there were commonalities in the causation theories he had offered in other cases. *Id.* at 74.

B. Dr. Chester V. Oddis

Dr. Oddis, a rheumatologist like Dr. Utz, testified for Respondent in support of the two expert reports he prepared. Tr. at 86-159; Report, dated September 27, 2018, filed as Ex. A (ECF No. 29-1) ("First Oddis Rep."); Report, dated July 15, 2019, filed as Ex. F (ECF No. 37-1) ("Second Oddis Rep."). He proposed that (contrary to Dr. Utz's view) Petitioner never fully manifested RA, and his condition was better described as "preclinical RA," with some evidence of reactive symptoms around the time he received the flu vaccine. Tr. at 93-94.

Dr. Oddis is board-certified in internal medicine and rheumatology Tr. at 88; Oddis CV, filed as Ex. B (ECF No. 29) ("Oddis CV"). He is presently a Professor of Medicine in the Division of Rheumatology and Clinical Immunology in the School of Medicine at the University of Pittsburgh. Tr. at 87. He received his undergraduate degree from the University of Pittsburgh and his medical degree from Pennsylvania State University School of Medicine. *See* Oddis CV. Dr. Oddis specializes in the treatment of idiopathic inflammatory myopathies, although he also has expertise in treatment of RA and interstitial lung disease. Tr. at 88. In addition to his teaching duties, Dr. Oddis maintains a clinical practice. *Id.* Dr. Oddis testified that he sees patients at the University of Pittsburgh clinic weekly. *Id.* at 89. His clinical practice includes all rheumatologic diseases, including RA and preclinical RA. *Id.* at 88-89.

[15] *See,* e.g., *Tullio v. Sec'y of Health & Human Servs.,* No. 15-51V, 2019, WL 7580149 (Fed. Cl. Spec. Mstr. Dec. 19, 2019) (flu vaccine did not cause development of RA), *aff'd*, 2020 WL 4593161, slip op. (Fed. Cir. 2020); *Parker v. Sec'y of Health & Human Servs.*, No. 14-979V, 2019 WL 3425297 (Fed. Cl. Spec. Mstr. June 24, 2019).

Dr. Oddis's overview of RA was largely consistent with Dr. Utz's testimony. He described RA as an inflammatory-driven arthritis that can insidiously progress over time, although its clinical manifestations are "heterogeneous." Tr. at 94. He distinguished noninflammatory joint pain, or arthralgia, from pain *with* inflammation, which would be properly characterized as arthritis. *Id.* at 153. RA will feature most often "a symmetric small joint inflammatory arthropathy" that is observed to be abnormal on exam as well as in lab test results. *Id.* at 95, 145. Such testing includes looking for the presence of rheumatoid factor and anti-CCP antibodies, as well as evidence of inflammation biomarkers (e.g., high erythrocyte sedimentation rates or [CRP]). *Id.* A family history of RA can suggest a genetic predisposition toward developing RA. *Id.* at 101. Dr. Oddis also emphasized the role of smoking, adding that it plus family history were especially significant risk factors in tandem. *Id.* at 127. Many things could possibly trigger RA (viruses or environmental pollutants, for example – as well as a vaccine in a "susceptible host"), but more research was required to shed light on what triggers were pathologically meaningful. Tr. at 159.

Unlike Dr. Utz, however, Dr. Oddis endorsed the view that preclinical RA is also a reasonable diagnostic classification.[16] He deemed preclinical RA to be a "relatively new," not fully-defined concept that medical science had only been considering for the past seven to eight years (although he has seen 20 to 25 patients that he felt fit the designation). *Id.* at 97-98. Dr. Oddis also cited literature specifically discussing the concept. *Id.* at 102-03; K. Deane et al., *Pathogenesis and Prevention of Rheumatic Disease: Focus on Preclinical RA and SLE*, 10 Nat. Rev. Rheumatol. 212-228 (2014), filed as Ex. C on September 28, 2018 (ECF No. 29) ("Deane I").

Dr. Oddis defined preclinical RA as "a period of detectable autoimmunity" prior to actual manifestation of common RA symptoms. Tr. at 96. A patient may have a number of nonspecific symptoms, like generalized/migratory aches and pains, and may also present with some limited clinical features (such as a single swollen joint) that might support an RA diagnosis later, but will also test positive serologically for anti-CCP antibodies, rheumatoid factor, etc. *Id.* at 96-97, 98, 142-43. Such a presentation may (erroneously) encourage an RA diagnosis, even where the individual does not truly meet the classification criteria. *Id.* at 104; Deane I at 213. Treatment aims to follow the patients and monitor whether their symptoms develop into "full-blown RA." *Id.* at 100. In Dr. Oddis's experience, only ten percent of such individuals see their symptoms progressively evolve in this manner. *Id.* at 100, 144. How preclinical RA actually does evolve into classic RA is something that has not been fully evaluated by medical science. Tr. at 104. However, Dr. Oddis noted that the increased presence of the anti-CCP antibodies over time was likely integral to RA's eventual progression. *Id.* at 131 (citing A. Willemze et al., *The influence of ACPA Status and Characteristics on the Course of RA*, 8(2) RA. Nat. Rev. Rheumatol. 144-142 (2012), filed as Ex. E on September 28, 2018, (ECF No. 29).

[16] Dr. Utz agreed with this somewhat, but testified that use of the term "preclinical RA" can cause confusion. Tr. at 26. Rather, in Dr. Utz's view it was only proper to employ the preclinical RA diagnosis if the patient actually has RA. *Id.* Dr. Utz further explained that saying a patient has preclinical RA because they have a positive CCP test implies that they are going to develop RA, which is not necessarily true. *Id.*

Dr. Oddis expressed the firm opinion, based on his review of the medical records, that Mr. Hock was most accurately diagnosed with only preclinical RA (with some evidence of reactive arthritis around the time of vaccination as well). Tr. at 94, 156. Petitioner had presented with complaints of joint pain consistently in his history, leading treaters to prescribe RA-directed medication likely to ameliorate it, and his testing results reasonably suggested to treaters that the later development of RA was a concern. Tr. at 124. However, Dr. Oddis disputed that Petitioner ever "really had a symmetric inflammatory joint – arthropathy" consistent with RA. *Id; see also* Tr. at 155 (emphasizing Petitioner's failure to ever develop a "symmetric small joint problem"). Rather, the evidence of joint involvement had greatly *diminished* over Petitioner's course of treatment, along with evidence of inflammation. *Id.* At the same time, Petitioner had early on in his treatment tested positive for a number of RA-associated biomarkers, like anti-CCP antibodies, which he likely had possessed prior to vaccination (as Dr. Utz conceded). *Id.* at 130. These kinds of serologic findings were a core finding in support of a preclinical RA diagnosis. *Id*.

To illustrate the basis for his opinion, Dr. Oddis reviewed Petitioner's medical history. Mr. Hock's presenting symptoms at his October 24, 2015 ER visit appeared "nonspecific" to Dr. Oddis, and not strong indicia of RA in its "classic presentation." Tr. at 106. The initial treater concerns were that Petitioner had an infectious arthritis or cellulitis – a condition distinguishable from RA, and featuring "inflammation of the soft tissue," in this case near the joint, but not *of* it (as would be the case with RA). *Id.* at 107.

Dr. Oddis allowed for the likelihood that Petitioner's initial presentation might reflect a reactive arthritis. Tr. at 156-57. Dr. Oddis tended to discount, however, the statements from an initial treater that the flu vaccine had some association with Petitioner's presenting symptoms, observing that the actual medical record better supported the conclusion that this association was a product of the Petitioner's medical history recitation (which likely focused on the recency of the vaccination) rather than the treater's reasoned view. *Id.* at 108-09; Ex. 2 at 14. He did not dispute the possibility of vaccine involvement in these first, arthritis-like symptoms, but maintained that even if this were the case, Petitioner's *subsequent* course could not also be vaccine-attributed (and certainly the biomarkers Petitioner initially tested positively for could not themselves be due to vaccination). Tr. at 157.

The records from Mr. Hock's late-October hospitalization (October 24-26 2015), Dr. Oddis continued, revealed that his right ankle aspiration resulted in "no substantive findings," and specifically no inflammation, even though the ankle appeared to be "the most dramatically involved joint" in terms of Petitioner's overall presentation. Tr. at 109, 112. His white blood cell count was elevated, although Dr. Oddis allowed this could be the byproduct of steroidal medication he had received (and in fact treater notes confirm this presumption). *Id.* at 109-110; Ex. 2 at 16. Testing performed when Petitioner was again hospitalized less than a week later (October 30th) seemed to confirm an RA diagnosis, given the biomarker findings (rheumatoid factor, anti-CCP antibodies), but Dr. Oddis proposed that this did not fully take into account Petitioner's "atypical presentation." Tr. at 111.

Dr. Oddis also highlighted Dr. Gadzhiev's exam in December 2015 (Petitioner's first meeting with a rheumatology specialist), by which time Dr. Gadzhiev had the benefit of review of Petitioner's records and history to that date. Tr. at 111-13. Dr. Oddis interpreted Dr. Gadzhiev's comments to mean that he did not in fact believe Petitioner actually had RA at that time, and was more concerned with a monitoring process given the warning signs (like the blood test results and Petitioner's history), although Methotrexate – a drug commonly used to treat RA – was then prescribed. *Id.* at 113-16. Indeed, Dr. Gadzhiev merely proposed that Petitioner follow up with him in six months. *Id.* at 112, 113. At most, Dr. Gadzhiev had opined that Petitioner had experienced a reactive arthritis not long after vaccination that had resolved. *Id.* at 114.

The subsequent medical records for 2016 were also, in Dr. Oddis's view, consistent with his conclusion that Petitioner had not yet developed RA. At a visit in early January 2016 with an orthopedist, for example, Mr. Hock was "not demonstrating any active inflammatory response" despite complaints of left ankle pain, there was no evidence of inflammation biomarkers, and further aspiration was deemed unnecessary. Tr. at 116-18; Ex. 3 at 226. And after another hospitalization around the same time, the discharge summary suggested treaters harbored only a "low suspicion" for RA, and seemed more focused on treating an infectious process that might have caused cellulitis – as noted by Dr. Oddis, the examining orthopedic surgeon did not observe any significant inflammation at that time. Tr. at 118. Indeed, Petitioner was then told to hold off on arthritis medication in order to allow the antibiotic treatments to work. *Id.* at 119.

Going forward in the record, Dr. Oddis noted other instances in which he felt the evidence for RA was weak or inconclusive. Tr. at 119-21; Ex. 3 at 184 (January 21, 2016 treatment note) and 187 ("no evidence for any convincing inflammatory arthropathy"). A later treatment note from an October 2016 rheumatology consult observed that Petitioner's arthritis was "non-erosive," and although Petitioner continued to complain of pain, his presentation was atypical, there remained no evidence of an ongoing inflammatory process, and the exam findings overall were deemed by treaters to be "underwhelming." Tr. at 122; Ex. 3 at 67-69.

Based upon Petitioner's overall presentation, plus what was known about his risk factors (both a family history of RA and personal history of smoking), Dr. Oddis proposed that he would have been less willing to diagnose Petitioner with RA. Tr. at 128-29. Rather, he would have preferred to watch and see if Petitioner continued to manifest "the more classic features of [RA] after that initial presentation [in October 2015]." *Id.* at 128. Here, that did not occur – "at no point thereafter did [Petitioner] ever really have another swollen joint" or "significant joint inflammation." *Id.* As a result, Petitioner's overall course would have led Dr. Oddis to take more care in prescribing RA medications. *Id.* at 129.

Dr. Oddis acknowledged the record evidence indicating treater support for an RA diagnosis, but overall expressed skepticism of their conclusions, maintaining that they appeared to have "latched on" to an RA diagnosis simply on the basis of blood testing results (which he had

previously noted only supported the preclinical RA diagnosis in his view, absent certain other clinical proof). Tr. at 146-48. He maintained this position despite evidence shown to him on cross from March 2016, which seemed to establish right wrist joint swelling, deeming this merely a "piece of the puzzle" that ultimately did not merit much weight (since it later resolved). *Id.* at 148-49; Ex. 4 at 24.

In contesting whether Petitioner had accurately been diagnosed with RA, Dr. Oddis questioned Dr. Utz's invocation of the relevant classification criteria. Tr. at 125-30. He emphasized (as Dr. Utz had acknowledged) that the criteria were mainly generated for the purpose of standardizing how subjects would be classified for purposes of their participation in clinical trials, rather than for pure diagnostic reasons (even if the criteria do get used sometime for that purpose), and that making an accurate RA diagnosis required clinical expertise rather than simply rote application of these criteria. *Id.* at 125, 146. He also admitted that they were underinclusive, in order to more likely identify those individuals who in fact "have the disease," (*Id.* at 126).

Dr. Oddis nevertheless maintained that Dr. Utz had taken "a little bit of liberty" in concluding that sufficient criteria were met in Petitioner's case to meet the EULAR or American College of Rheumatology standards. Tr. at 125, 133. In particular, Dr. Oddis did not agree that Petitioner displayed the necessary "degree of joint involvement." *Id.* He also questioned Dr. Utz's proposal that but for steroid treatment (which could mask symptoms) Petitioner would more obviously satisfy the criteria. *Id.* He ultimately did not accept that Petitioner's overall history met the six-point EULAR threshold. *Id.* at 155; *see also* Tr. at 156 (Petitioner "would not be enrolled in a clinical trial as having rheumatoid arthritis" under the criteria).

In addition to his testimony interpreting Petitioner's history and calling into question whether it truly supported an RA diagnosis, Dr. Oddis contested that the flu vaccine could even cause RA, or did so to Petitioner. Tr. at 141. He disputed that the vaccine was deemed a risk factor by rheumatologists, observing (as had Dr. Utz) that it was generally administered to RA patients due to the greater risk posed by the effects of a wild influenza infection. *Id*. at 129-30. Dr. Oddis only allowed for the possibility that the flu vaccine (like its wild virus counterpart) could cause transient malaise or pain akin to what Petitioner reported in October 2015, but added that any inflammation associated with it would resolve in short course, and thus not establish the onset of RA. *Id.* at 140-41. Dr Oddis firmly denied that the flu vaccine could specifically cause the anti-CCP antibodies to develop – especially since they likely existed here at the time of Petitioner's vaccination (and could not have generated within 24 hours of vaccination). *Id.* at 134, 158. And he challenged Dr. Utz's assertions that DR4 molecule positivity supported his mechanistic explanation for the progression of Petitioner's alleged RA, noting that the record did not in fact establish that Petitioner was DR4-positive. *Id.* at 136.[17] He agreed, however, that Mr. Hock did

[17] Because Dr. Oddis is not an immunology specialist, and because Dr. Rose (who possessed such credentials in abundance) testified for Respondent on such matters, I do not herein include recitation or discussion of Dr. Oddis's testimony on such matters, which clearly lay a bit outside of his actual expertise. Tr. at 137-38.

not display joint-related pain complaints before receiving the flu vaccine in October 2015. Tr. at 142.

C. Dr. Noel Rose[18]

Dr. Rose provided an opinion for Respondent on immunologic issues raised in this case. Tr. at 160-205; Report, filed July 22, 2019, marked as Ex. H (ECF No. 37-3) ("Rose Rep."). He opined that although elements of Petitioner's theory (such as molecular mimicry as a mechanism for explaining autoimmune pathologic processes) have scientific validity, there is no reliable scientific or medical support for the conclusion that the flu vaccine could cause or trigger RA, regardless of the proposed mechanism. Rose Rep. at 8.

Dr. Rose is board certified in pathology, medical microbiology, and laboratory immunology. *See* Curriculum Vitae of Dr. Rose, dated July 22, 2019, filed as Ex. I (ECF No. 37-4) ("Rose CV"). He received his Ph.D. at the University of Pennsylvania, and his medical degree from State University of New York after attending Yale University for his undergraduate education. *See* Rose CV; Tr. at 160. At the time of hearing, Dr. Rose was serving part-time on the faculty of Department of Pathology at Brigham & Women's Hospital, and as senior lecturer at Harvard Medical School. Tr. at 161. He was previously chair of the department of immunology and infectious diseases at Johns Hopkins University, and director of the World Health Organization Collaborating Center for Autoimmune Disorders. Rose CV at 1; Tr. at 161. Dr. Rose has authored over 500 publications in scientific journals and books devoted to autoimmune diseases. Rose CV at 5; Tr. at 162. His focus over his career was on the functioning of the immunologic system, the pathogenesis and nature of autoimmune diseases, and "clinical applications" for diagnosis and treatment of the same. Tr. at 161.

Dr. Rose began by discussing the general concept of molecular mimicry, largely agreeing with Dr. Utz's description and accepting its overall soundness as a medical/scientific theory. Tr. at 164, 169. In particular, he agreed that it provided a reasonable way to understand the pathogenic mechanisms by which an autoimmune disease might progress. *Id.* at 187. However, he also characterized it as "at best a plausible mechanism exploring the role of infection and vaccines," (Rose Rep. at 8) and at hearing he proposed that the scientific community today placed less importance in it than when the concept was first proposed. Tr. at 188; *see also* Tr. at 164-65 (molecular mimicry provides a "way of tying together a vaccine and adverse outcome"). To illustrate how molecular mimicry is understood by medical science to work, Dr. Rose referenced rheumatic fever - an inflammatory disease that occurs most often in the young.[19] Rheumatic fever is usually preceded by a streptococcal (bacterial) infection in the throat. *Id.* at 165. Antigens on

[18] Dr. Rose sadly passed away in July 2020.

[19] Rheumatic fever is a febrile disease occurring as a delayed sequela of infections with group A beta-hemolytic streptococci, characterized by multiple focal inflammatory lesions of connective tissue, especially of the heart, blood vessels, and joints; other manifestations include sudden fever, joint pain, abdominal pain, and Sydenham chorea. *Dorland's* at 687.

the surface of that bacterium are also present in certain heart structure cells, such that the body's immune response in attacking the strep infection can also result in a cross-reactive autoimmune attack on the heart. *Id.* at 165-66.

Dr. Rose noted, however, that the mere *possibility* of antigenic similarity between a presenting virus (or vaccine) and host structure did not mean that it was likely to occur, let alone cause disease. Tr. at 191. "There are many, many cross-reactions in nature," making it relatively easy to identify mimics, but the existence of widespread structural or sequential homology did not mean that an autoimmune response always occurred in the existence of identified mimicry. *Id.* at 170-71, 183-84, 188 ("just finding molecular mimicry is about at useful as buying . . . a lottery ticket at the local drug store"). He also referenced literature that demonstrated how "very, very common" antigenic similarity was, given the limited number of amino acids comprising all proteins in nature. Tr. at 182-83; A. Markarkov, *Plant-Derived Virus-Like Particle Vaccines Drive Cross-Presentation of Influenza A Hemagglutinin Peptides by Human Monocyte-Derived Macrophages*, 4:17 npj Vaccines 1-12 (2019), filed as Ex. O on November 26, 2019, (ECF No. 48-6); J. Xu et al., *Evolutionary History and Phylodynamics of Influenza A and B Neuraminidase (NA) Genes Inferred from Large-Scale Sequence Analyses*, 7(7) Evolutionary Dynamics of Influenza Neuraminidase 1-15 (2012), filed as Ex. P on November 26, 2019 (ECF No. 48-7) ("Xu").

Rather, for molecular mimicry to result in an autoimmune cross-reaction sufficient to be pathogenic, "there must be heightened affinity" between the cross-reactive cell and self antigenic target. Tr. at 184; E. Ossipova et al., *Affinity Purified Anti-Citrullinated Protein/Peptide Antibodies Target Antigens Expressed in the Rheumatoid Joint*, 16 Arthritis Research & Therapy 1-11 (2014), filed as Ex. T on November 26, 2019 (ECF No. 48-11). Such affinity could be shown in the context of the autoimmune attack that anti-CCP antibodies had with collagen – but Dr. Utz's theory did not similarly present any scientific or medical evidence suggesting that the flu vaccine's antigens were also *likely* to so bind, let alone encourage that process in other ways (and as noted above Dr. Utz freely admitted he could not substantiate this component of his theory).

The flu virus, Dr. Rose stated, "almost certainly" also can be shown to have antigens with sufficient homology to self structures such that they could theoretically (via an immune response) initiate a cross-reaction against "counterpart antigens in the body." Tr. at 166. And Dr. Rose acknowledged that the flu vaccine had been demonstrated (after the 1977 swine flu epidemic) to have the same capacity, due to molecular mimicry, to increase the occurrence of Guillain-Barré syndrome ("GBS"), adding that this had been corroborated with "provocative epidemiologic evidence." *Id.* at 167.

However, Dr. Rose disputed that any similar-such reliable or persuasive evidence existed that would associate the flu vaccine with RA. Tr. at 168. Dr. Utz himself had not found any such evidence despite his own RA expertise. *Id.* Given the vast number of people who suffer from RA and likely also have received the flu vaccine, Dr. Rose would have expected an association to reveal itself in the data if it had validity. *Id.* at 169. There was thus in his estimation insufficient evidence to accept Petitioner's assertion that the flu vaccine could cause RA via the mechanism of

molecular mimicry. *Id.* at 170. He also observed that medical science recognized the importance of vaccinating persons with a chronic disease like RA. *Id.* at 181-82; *see also* V. Gosselin Boucher et al. *Interventions to Improve Vaccine Acceptance Among Rheumatoid Arthritis Patients: a Systemic Review*, 38 Clinical Rheumatol. 1537-1544 (2019), filed as Ex. W on November 26, 2019, (ECF No. 48-13).

Dr. Rose went on to review other elements of Dr. Utz's opinion that he disputed. He acknowledged that it was scientifically difficult to establish molecular mimicry in explaining any disease process, requiring the need to look for indirect proof of it. Tr. at 172. Dr. Utz did so, he recounted, by suggesting "the link between an initial innate response . . . or perhaps better characterized as innate inflammation on the one hand with an antibody or self-reactive T cell that could be the cause of disease." *Id.* This process, in Dr. Utz's telling, would then have a third stage – "the development of an antibody or T cell or both" that would directly cause harm to the collagen in the joints. *Id.* at 173.

Overall, Dr. Rose characterized Dr. Utz's three-stage immune response theory for associating the flu vaccine with RA as an "ingenious suggestion" worthy of study – but he denied it had reliable evidentiary support. Tr. at 173, 196 (Mr. Hock "can't be the only guy in the world who has these three steps"), 197, 201-02. He noted in particular that the intermediate/second leg of Dr. Utz's theory (bystander activation of autoreactive T cells) was a "very good idea," but he doubted (except in an animal experiment that was structured to look narrowly at the issue) that inflammation initiated by the innate immune system would in turn cause the release the chemokines[20] or other immune cells necessary to attract the autoreactive T cells' involvement, and questioned whether any science demonstrated this as having ever occurred in connection with RA. Tr. at 203, 204 ("I don't know enough what gets them together so you would get the handoff" from the innate response to bystander activation).

Dr. Rose's attack on Dr. Utz's theory also arose from the theory's conception of how the immune response would generally unfold. Dr. Rose noted that some kind of outside insult or injury could initiate an immunologic innate response, resulting in inflammation, but that this process would typically last only a few days, and would usually be "tightly controlled" by a person's immune system. Tr. at 174. Only in "exceptional circumstances" would it persist longer. *Id.* at 175.[21] But it would have to persist for an unusual length of time for the bystander stage of Dr. Utz's theory to come into being. *Id.* at 204. The second and third stages of the Petitioner's theory would also require that the "same individual" with the propensity for an extended inflammation

[20] Chemokines are low-molecular-weight (8-10 kD) cytokines that induce chemotaxis or chemokinesis in leukocytes (or in particular populations of leukocytes). *Dorland's* at 335. Chemokines act as regulators of the immune system, and may also play roles in the circulatory and central nervous system. *Id.*

[21] Dr. Rose invoked the "cytokine storm" concept to illustrate what a persistent, cytokine-driven innate immune response would look like, but noted in so doing that the process would be accompanied by obvious clinical manifestations not present here. Tr. at 204-05 ("you don't see that, if the patient has his problems with his knee and his ankle, but he doesn't have cytokine storm. You don't have a lot of cytokines being produced here").

process also experience further unusual immune processes – further diminishing the theory's likelihood. *Id.* at 176; Rose Rep. at 5.

The flu vaccine itself, Dr. Rose proposed, was actually unlikely to act in a manner consistent with Dr. Utz's theory. Many vaccines were intended to be given to a person prior to their exposure to the relevant wild virus or bacterial antigen, so that the vaccine would produce memory immune cells that would in the future recognize the relevant pathogenic antigen. Tr. at 179. The immunity conferred by such vaccines can take longer to obtain – and in fact the process of "teaching" memory T cells takes several days to weeks. *Id.* at 178-79.

The flu vaccine, by contrast, has to be updated each year, in light of guesses its manufacturers make about the most likely wild virus strain in a pending flu season, meaning it must be designed "with a relatively rapid response." Tr. at 180, 186 ("this is a vaccine for quick in and quick out"). To that end, it is designed to "favor[] the B cell" and provoke faster production of antibodies specific to the vaccine antigens relevant to the flu wild virus strain thought to be prevalent. It was therefore unlikely to cause the "good memory response" that Dr. Utz's theory required, or to render the production of specific T cells. *Id.* at 180, 192; Rose Rep. at 4.

Dr. Rose also challenged the timeframe in which the flu vaccine had allegedly initiated Petitioner's RA. A timeframe of 24 hours, he maintained, was too short in which "the process of antibody appearance, replication, development and the carrying forth of methods of pathology to produce" RA could reasonably be expected to occur. Tr. at 171. The mere creation of antibodies alone was not enough to have a pathologic impact – those antibodies would then require time to cause manifestations of symptoms. *Id.* at 172. What was known about the association between the flu vaccine and GBS (based on the 1977 evidence) suggested a 15-day timeframe on average from immunization to disease in that case – longer than the single day of onset at issue in this case. *Id.*

III. *Procedural History*

As stated at the outset of this Decision, the Petition was initiated in the winter of 2017. The Rule 4(c) Report opposing compensation was filed in September 2017 (ECF No. 16), and then the parties began the process of filing their respective expert reports from the aforementioned individuals. Once expert briefing was largely completed by the late summer of 2019, I established a pretrial schedule, with the entitlement hearing in this matter originally set for March 5, 2020. ECF No. 42. The hearing was subsequently rescheduled for March 12, 2020, and the matter went forward to trial. The parties opted against the filing of post-hearing briefs, and the matter is now ripe for resolution.

IV. *Applicable Law*

A. General Standards of Proof

To receive compensation in the Vaccine Program, a petitioner must prove either: (1) that he suffered a "Table Injury"—i.e., an injury falling within the Vaccine Injury Table—corresponding to one of the vaccinations in question within a statutorily prescribed period of time or, in the alternative, (2) that his illnesses were actually caused by a vaccine (a "Non-Table Injury"). *See* Sections 13(a)(1)(A), 11(c)(1), and 14(a), as amended by 42 C.F.R. § 100.3; § 11(c)(1)(C)(ii)(I); *see also Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1321 (Fed. Cir. 2010); *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1320 (Fed. Cir. 2006).[22] In this case, Petitioner does not assert a Table claim.

For both Table and Non-Table claims, Vaccine Program petitioners bear a "preponderance of the evidence" burden of proof. Section 13(1)(a). That is, a petitioner must offer evidence that leads the "trier of fact to believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the judge of the fact's existence." *Moberly*, 592 F.3d at 1322 n.2; *see also Snowbank Enter. v. United States*, 6 Cl. Ct. 476, 486 (1984) (mere conjecture or speculation is insufficient under a preponderance standard). Proof of medical certainty is not required. *Bunting v. Sec'y of Health & Human Servs.*, 931 F.2d 867, 873 (Fed. Cir. 1991). In particular, a petitioner must demonstrate that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly*, 592 F.3d at 1321 (quoting *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352–53 (Fed. Cir. 1999)); *Pafford v. Sec'y of Health & Human Servs.*, 451 F.3d 1352, 1355 (Fed. Cir. 2006). A petitioner may not receive a Vaccine Program award based solely on his assertions; rather, the petition must be supported by either medical records or by the opinion of a competent physician. Section 13(a)(1).

In attempting to establish entitlement to a Vaccine Program award of compensation for a Non-Table claim, a petitioner must satisfy all three of the elements established by the Federal Circuit in *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (2005) : "(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."

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

[22] Decisions of special masters (some of which I reference in this ruling) constitute persuasive but not binding authority. *Hanlon v. Sec'y of Health & Human Servs.*, 40 Fed. Cl. 625, 630 (1998). By contrast, Federal Circuit rulings concerning legal issues are binding on special masters. *Guillory v. Sec'y of Health & Human Servs.*, 59 Fed. Cl. 121, 124 (2003), *aff'd* 104 F. Appx. 712 (Fed. Cir. 2004); *see also Spooner v. Sec'y of Health & Human Servs.*, No. 13-159V, 2014 WL 504728, at *7 n.12 (Fed. Cl. Spec. Mstr. Jan. 16, 2014).

Petitioners may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1378–79 (Fed. Cir. 2009) (citing *Capizzano*, 440 F.3d at 1325–26). Special masters, despite their expertise, are not empowered by statute to conclusively resolve what are essentially thorny scientific and medical questions, and thus scientific evidence offered to establish *Althen* prong one is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's preponderant evidence standard." *Id.* at 1380. Accordingly, special masters must take care not to increase the burden placed on petitioners in offering a scientific theory linking vaccine to injury.

In discussing the evidentiary standard applicable to the first *Althen* prong, the Federal Circuit has consistently rejected the contention that it can be satisfied merely by establishing the proposed causal theory's scientific or medical *plausibility*. *See Boatmon v. Sec'y of Health & Human Servs.*, 941 F.3d 1351, 1359 (Fed. Cir. 2019); *see also LaLonde v. Sec'y of Health & Human Servs.*, 746 F.3d 1334, 1339 (Fed. Cir. 2014) ("[h]owever, in the past we have made clear that simply identifying a 'plausible' theory of causation is insufficient for a petitioner to meet her burden of proof." (citing *Moberly*, 592 F.3d at 1322)). Petitioners otherwise always have the ultimate burden of establishing their *overall* Vaccine Act claim with preponderant evidence, regardless of what evidentiary level of evidence on the "can cause" prong is required. *W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1356 (Fed. Cir. 2013) (citations omitted); *Tarsell v. United States*, 133 Fed. Cl. 782, 793 (2017) (noting that *Moberly* "addresses the petitioner's overall burden of proving causation-in-fact under the Vaccine Act" by a preponderance standard).

The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375–77; *Capizzano*, 440 F.3d at 1326; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). In establishing that a vaccine "did cause" injury, the opinions and views of the injured party's treating physicians are entitled to some weight. *Andreu*, 569 F.3d at 1367; *Capizzano*, 440 F.3d at 1326 ("medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury'") (quoting *Althen*, 418 F.3d at 1280). Medical records are generally viewed as particularly trustworthy evidence, since they are created contemporaneously with the treatment of the patient. *Cucuras v. Sec'y of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993).

Medical records and statements of a treating physician, however, do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. Section 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 746 n.67 (2009) ("there is nothing . . . that mandates that the testimony of a treating physician is sacrosanct—that it must be accepted in its entirety and cannot be rebutted"). As with expert testimony offered to establish a theory of causation, the

opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases. The views of treating physicians should be weighed against other, contrary evidence also present in the record—including conflicting opinions among such individuals. *Hibbard v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 742, 749 (2011) (not arbitrary or capricious for special master to weigh competing treating physicians' conclusions against each other), *aff'd*, 698 F.3d 1355 (Fed. Cir. 2012); *Veryzer v. Sec'y of Dept. of Health & Human Servs.*, No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011), *mot. for review denied*, 100 Fed. Cl. 344, 356 (2011), *aff'd without opinion*, 475 F. Appx. 765 (Fed. Cir. 2012).

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *de Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must align with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *Id.* at 1352; *Shapiro v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 532, 542 (2011), *recons. denied after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem.*, 503 F. Appx. 952 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Human Servs.*, No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for rev. denied* (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

B. Legal Standards Governing Factual Determinations

The process for making determinations in Vaccine Program cases regarding factual issues begins with consideration of the medical records. Section 11(c)(2). The special master is required to consider "all [] relevant medical and scientific evidence contained in the record," including "any diagnosis, conclusion, medical judgment, or autopsy or coroner's report which is contained in the record regarding the nature, causation, and aggravation of the petitioner's illness, disability, injury, condition, or death," as well as the "results of any diagnostic or evaluative test which are contained in the record and the summaries and conclusions." Section 13(b)(1)(A). The special master is then required to weigh the evidence presented, including contemporaneous medical records and testimony. *See Burns v. Sec'y of Health & Human Servs.*, 3 F.3d 415, 417 (Fed. Cir. 1993) (it is within the special master's discretion to determine whether to afford greater weight to contemporaneous medical records than to other evidence, such as oral testimony surrounding the events in question that was given at a later date, provided that such determination is evidenced by a rational determination).

Medical records that are created contemporaneously with the events they describe are presumed to be accurate and "complete" (i.e., presenting all relevant information on a patient's health problems). *Cucuras*, 993 F.2d at 1528; *Doe/70 v. Sec'y of Health & Human Servs.*, 95 Fed. Cl. 598, 608 (2010) ("[g]iven the inconsistencies between petitioner's testimony and his

contemporaneous medical records, the special master's decision to rely on petitioner's medical records was rational and consistent with applicable law"), *aff'd sub nom. Rickett v. Sec'y of Health & Human Servs*., 468 F. Appx. 952 (Fed. Cir. 2011) (non-precedential opinion). This presumption is based on the linked propositions that (i) sick people visit medical professionals; (ii) sick people honestly report their health problems to those professionals; and (iii) medical professionals record what they are told or observe when examining their patients in as accurate a manner as possible, so that they are aware of enough relevant facts to make appropriate treatment decisions. *Sanchez v. Sec'y of Health & Human Servs.*, No. 11-685V, 2013 WL 1880825, at *2 (Fed. Cl. Spec. Mstr. Apr. 10, 2013); *Cucuras v. Sec'y of Health & Human Servs.*, 26 Cl. Ct. 537, 543 (1992), *aff'd*, 993 F.2d at 1525 (Fed. Cir. 1993) ("[i]t strains reason to conclude that petitioners would fail to accurately report the onset of their daughter's symptoms").

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

There are, however, situations in which compelling oral testimony may be more persuasive than written records, such as where records are deemed to be incomplete or inaccurate. *Campbell v. Sec'y of Health & Human Servs*., 69 Fed. Cl. 775, 779 (2006) ("like any norm based upon common sense and experience, this rule should not be treated as an absolute and must yield where the factual predicates for its application are weak or lacking"); *Lowrie*, 2005 WL 6117475, at *19 ("'[w]ritten records which are, themselves, inconsistent, should be accorded less deference than those which are internally consistent'") (quoting *Murphy*, 23 Cl. Ct. at 733)). Ultimately, a determination regarding a witness's credibility is needed when determining the weight that such testimony should be afforded. *Andreu*, 569 F.3d at 1379; *Bradley v. Sec'y of Health & Human Servs*., 991 F.2d 1570, 1575 (Fed. Cir. 1993).

When witness testimony is offered to overcome the presumption of accuracy afforded to contemporaneous medical records, such testimony must be "consistent, clear, cogent, and compelling." *Sanchez*, 2013 WL 1880825, at *3 (citing *Blutstein v. Sec'y of Health & Human Servs*., No. 90-2808V, 1998 WL 408611, at *5 (Fed. Cl. Spec. Mstr. June 30, 1998)). In determining the accuracy and completeness of medical records, the Court of Federal Claims has listed four possible explanations for inconsistencies between contemporaneously created medical records and later testimony: (1) a person's failure to recount to the medical professional everything that happened during the relevant time period; (2) the medical professional's failure to document everything reported to her or him; (3) a person's faulty recollection of the events when presenting

testimony; or (4) a person's purposeful recounting of symptoms that did not exist. *Lalonde v. Sec'y of Health & Human Servs.*, 110 Fed. Cl. 184, 203-04 (2013), *aff'd*, 746 F.3d 1334 (Fed. Cir. 2014). In making a determination regarding whether to afford greater weight to contemporaneous medical records or other evidence, such as testimony at hearing, there must be evidence that this decision was the result of a rational determination. *Burns*, 3 F.3d at 417.

C. Analysis of Expert Testimony

Establishing a sound and reliable medical theory often requires a petitioner to present expert testimony in support of his claim. *Lampe v. Sec'y of Health & Human Servs.*, 219 F.3d 1357, 1361 (Fed. Cir. 2000). Vaccine Program expert testimony is usually evaluated according to the factors for analyzing scientific reliability set forth in *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 594–96 (1993). *See Cedillo v. Sec'y of Health & Human Servs.*, 617 F.3d 1328, 1339 (Fed. Cir. 2010) (citing *Terran v. Sec'y of Health & Human Servs.*, 195 F.3d 1302, 1316 (Fed. Cir. 1999)). "The *Daubert* factors for analyzing the reliability of testimony are: (1) whether a theory or technique can be (and has been) tested; (2) whether the theory or technique has been subjected to peer review and publication; (3) whether there is a known or potential rate of error and whether there are standards for controlling the error; and (4) whether the theory or technique enjoys general acceptance within a relevant scientific community." *Terran*, 195 F.3d at 1316 n.2 (citing *Daubert*, 509 U.S. at 592–95).

The *Daubert* factors play a slightly different role in Vaccine Program cases than they do when applied in other federal judicial fora (such as the district courts). *Daubert* factors are usually employed by judges (in the performance of their evidentiary gatekeeper roles) to exclude evidence that is unreliable and/or could confuse a jury. In Vaccine Program cases, by contrast, these factors are used in the *weighing* of the reliability of scientific evidence proffered. *Davis v. Sec'y of Health & Human Servs.*, 94 Fed. Cl. 53, 66–67 (2010) ("uniquely in this Circuit, the *Daubert* factors have been employed also as an acceptable evidentiary-gauging tool with respect to persuasiveness of expert testimony already admitted"). The flexible use of the *Daubert* factors to evaluate the persuasiveness and reliability of expert testimony has routinely been upheld. *See, e.g.*, *Snyder*, 88 Fed. Cl. at 742–45. In this matter (as in numerous other Vaccine Program cases), *Daubert* has not been employed at the threshold, to determine what evidence should be admitted, but instead to determine whether expert testimony offered is reliable and/or persuasive.

Respondent frequently offers one or more experts in order to rebut a petitioner's case. Where both sides offer expert testimony, a special master's decision may be "based on the credibility of the experts and the relative persuasiveness of their competing theories." *Broekelschen v. Sec'y of Health & Human Servs.*, 618 F.3d 1339, 1347 (Fed. Cir. 2010) (citing *Lampe*, 219 F.3d at 1362). However, nothing requires the acceptance of an expert's conclusion "connected to existing data only by the *ipse dixit* of the expert," especially if "there is simply too great an analytical gap between the data and the opinion proffered." *Snyder*, 88 Fed. Cl. at 743 (quoting *Gen. Elec. Co. v. Joiner*, 522 U.S. 136, 146 (1997)); *see also Isaac v. Sec'y of Health &*

Human Servs., No. 08-601V, 2012 WL 3609993, at *17 (Fed. Cl. Spec. Mstr. July 30, 2012), *mot. for rev. denied*, 108 Fed. Cl. 743 (2013), *aff'd*, 540 F. Appx. 999 (Fed. Cir. 2013) (citing *Cedillo*, 617 F.3d at 1339). Weighing the relative persuasiveness of competing expert testimony, based on a particular expert's credibility, is part of the overall reliability analysis to which special masters must subject expert testimony in Vaccine Program cases. *Moberly*, 592 F.3d at 1325–26 ("[a]ssessments as to the reliability of expert testimony often turn on credibility determinations"); *see also Porter v. Sec'y of Health & Human Servs*., 663 F.3d 1242, 1250 (Fed. Cir. 2011) ("this court has unambiguously explained that special masters are expected to consider the credibility of expert witnesses in evaluating petitions for compensation under the Vaccine Act").

Expert opinions based on unsupported facts may be given relatively little weight. *See Dobrydnev v. Sec'y of Health & Human Servs.*, 556 F. Appx. 976, 992–93 (Fed. Cir. 2014) ("[a] doctor's conclusion is only as good as the facts upon which it is based") (citing *Brooke Group Ltd. v. Brown & Williamson Tobacco Corp.*, 509 U.S. 209, 242 (1993) ("[w]hen an expert assumes facts that are not supported by a preponderance of the evidence, a finder of fact may properly reject the expert's opinion")). Expert opinions that fail to address or are at odds with contemporaneous medical records may therefore be less persuasive than those which correspond to such records. *See Gerami v. Sec'y of Health & Human Servs.*, No. 12-442V, 2013 WL 5998109, at *4 (Fed. Cl. Spec. Mstr. Oct. 11, 2013), *aff'd*, 127 Fed. Cl. 299 (2014).

D. Consideration of Medical Literature

Both parties filed medical and scientific literature in this case, but not every filed item factors into the outcome of this decision. While I have reviewed all the medical literature submitted in this case, I discuss only those articles that are most relevant to my determination and/or are central to Petitioner's case—just as I have not exhaustively discussed every individual medical record filed. *Moriarty v. Sec'y of Health & Human Servs.*, 844 F.3d 1322, 1328 (Fed. Cir. 2016) ("[w]e generally presume that a special master considered the relevant record evidence even though he does not explicitly reference such evidence in his decision") (citation omitted); *see also Paterek v. Sec'y of Health & Human Servs.,* 527 F. Appx. 875, 884 (Fed. Cir. 2013) ("[f]inding certain information not relevant does not lead to—and likely undermines—the conclusion that it was not considered").

E. Consideration of Comparable Special Master Decisions

In reaching a decision in this case, I have considered other decisions issued by special masters (including my own) involving similar injuries, vaccines, or circumstances. I also reference some of those cases in this Decision, in an effort to establish common themes, as well as demonstrate how prior determinations impact my thinking on the present case.

There is no error in doing so. It is certainly correct that prior decision in different cases do not *control* the outcome herein.[23] *Boatmon v. Sec'y of Health & Human Servs.,* 941 F.3d 1351, 1358–59 (Fed. Cir. 2019); *Hanlon v. Sec'y of Health & Human Servs.*, 40 Fed. Cl. 625, 630 (1998). Thus, the fact that another special master reasonably determined elsewhere, on the basis of facts not in evidence in this case, that preponderant evidence supported the conclusion that vaccine X caused petitioner's injury Y does not compel me to reach the same conclusion in *this* case. Different actions present different background medical histories, different experts, and different items of medical literature, and therefore can reasonably result in contrary determinations.

However, it is *equally* the case that special masters reasonably draw upon their experience in resolving Vaccine Act claims. *Doe v. Sec'y of Health & Human Servs.,* 76 Fed. Cl. 328, 338–39 (2007) ("[o]ne reason that proceedings are more expeditious in the hands of special masters is that the special masters have the *expertise and experience to know the type of information that is most probative of a claim*") (emphasis added). They would therefore be remiss in ignoring prior cases presenting similar theories or factual circumstances, along with the reasoning employed in reaching such decisions. This is especially so given that special masters not only routinely hear from the same experts in comparable cases, but are also repeatedly offered the *same* items of medical literature regarding certain common causation theories. It defies reason and logic to obligate special masters to "reinvent the wheel," so to speak, in each new case before them, paying no heed at all to how their colleagues past and present have addressed similar causation theories or fact patterns. It is for this reason that prior decisions can have high persuasive value—and why special masters often explain how a new determination relates to such past decisions.[24] Even if the Federal Circuit does not *require* special masters to distinguish other relevant cases (*Boatmon,* 941 F.3d at 1358), it is still *wise* to do so.

ANALYSIS

I. *Overview of RA*

RA is a long-term autoimmune condition mainly affecting the joints. Its causes are thought to be a mix of immune, genetic, and environmental factors, but mechanistically it involves an

[23] By contrast, Federal Circuit rulings concerning legal issues are binding on special masters. *Guillory v. Sec'y of Health & Human Servs.*, 59 Fed. Cl. 121, 124 (2003), *aff'd* 104 F. Appx. 712 (Fed. Cir. 2004); *see also Spooner v. Sec'y of Health & Human Servs.*, No. 13-159V, 2014 WL 504728, at *7 n.12 (Fed. Cl. Spec. Mstr. Jan. 16, 2014). Special masters are also bound within a specific case by determinations made by judges of the Court of Federal Claims after a motion for review is resolved.

[24] Consideration of prior determinations is a two-way street that does not only inure to the benefit of one party. Thus, I would likely take into account the numerous decisions finding no association between vaccination and autism when confronted with a new claim asserting autism as an injury, and have informed such claimants early in the life of their case that the claim was not viable for just that reason. But I would *also* deem a non-Table claim asserting GBS after receipt of the flu vaccine as not requiring extensive proof on *Althen* prong one "can cause" matters, for the simple reason that the Program has repeatedly litigated the issue in favor of petitioners.

autoimmune attack on the synovial membranes of the joints, causing inflammation and later erosion and destruction of joint surfaces, along with deformity of affected joints. *See Dorland's Illustrated Medical Dictionary* 154 (33rd ed. 2020) ("*Dorland's*"); W. Arend et al., *Approach to the Patient with Rheumatic Disease* (2011), filed as Ex. 8.1 on August 7, 2019 (ECF No. 38-2) ("Arend") at 1648. RA can be "preclinical" in symptoms manifestation for a long period of time, with evidence of the biomarkers associated with it discerned well before a person first experiences outward symptoms. *See* K. Deane, *Preclinical Rheumatoid Arthritis (Autoantibodies): An Updated Review*, 16 Curr. Rheumatol. Rep. 419, 419 (2014) filed as Ex. D on September 9, 2018 (ECF No. 29-4), ("Deane II").

RA can trigger from a number of nonspecific inflammatory events. Arend at 1648. RA is known to be accompanied by the production of specific autoantibodies, including rheumatoid factor. *See* N. Rose et al., *The Autoimmune Diseases* 1185 (5th ed. 2014). The cellular components that are the target for the immune's systems attack in RA are thought to be collagen, fibrinogen, enolase, and vimentin. *Id.* Each of these proteins is sometimes harmed as a result of a process known as citrullination (in which the amino acid arginine is modified to citrulline). *See Olson v. Sec'y of Health & Human Servs.*, No. 13-439V, 2017 WL 3624085, at *5 (Fed. Cl. Spec. Mstr. July 14, 2017), *mot. for rev. denied*, 135 Fed. Cl. 670, 677 (2017), *aff'd*, 758 F. App'x 919 (Fed. Cir. 2018). Antibodies that respond to such citrullinated proteins are key to the autoimmune attack on joint tissues. *Id.*; Deane II at 421.

There are a number of risk factors associated with the development of RA, and they are consistent with what the experts discussed at hearing. Smoking is the most widely-recognized non-genetic risk factor and is strongly linked with the presence of the anti-CCP antibodies. *See* Tr. at 18. Genetic factors are also associated with RA. *Id.* It is also undisputed in this case that Mr. Hock has been shown to possess two of the autoantibody biomarkers strongly associated with RA – rheumatoid factor and anti-CCP antibodies.

There are several reasoned Program decisions discussing the association of the flu vaccine to RA. Most are not favorable to petitioners, however. *See, e.g.*, *Tullio v. Sec'y of Health & Human Servs.,* No. 15-51V, 2019, WL 7580149 (Fed. Cl. Spec. Mstr. Dec. 19, 2019) (flu vaccine did not cause development of RA), *aff'd*, 2020 WL 4593161, slip op. (Fed. Cir. 2020); *C.P. v. Sec'y of Health & Human Servs.*, No. 14-917V, WL 5483621 (Fed. Cl. Spec. Mstr. August 21, 2019) (flu vaccine did not cause development of polymyalgia and/or RA); *Parker v. Sec'y of Health & Human Servs*., No. 14-979V, 2019 WL 3425297 (Fed. Cl. Spec. Mstr. June 24, 2019) (flu vaccine did not cause development of RA and polyarticular inflammation); *but see Campbell v. Sec'y of Health & Human Servs.*, 97 Fed. Cl. 650 (2011) (finding entitlement for off-table claim that flu vaccine caused rheumatoid arthritis). Indeed, three of the four most-recent such decisions bear many similarities to this case (including two in which Dr. Utz offered a causation theory comparable to what he testified to in this matter).

In *Parker*, a petitioner alleged that the flu vaccine caused her to develop RA and polyarticular inflammation (with onset one day post vaccination), but the special master

responsible for the case denied entitlement. *Parker*, 2019 WL 3425297, at *3. As here, the *Parker* petitioner relied on Dr. Utz, who opined that Petitioner's RA was a direct result of receiving the flu vaccine, positing molecular mimicry as the primary mechanism. *Id.* at * 16. Dr. Utz theorized that the petitioner would have been exposed to influenza viruses and related antigens during her lifetime, and likely had a memory immune response in which preexisting memory B and T cells were activated by the vaccine *Id.* at *17.

But the *Parker* claimant did not reliably establish RA could occur via vaccine-caused molecular mimicry, no evidence was presented that vaccination causes autoimmune cross-reactions to cause RA, and Dr. Utz's assertion that this cross-reaction occurs and induces RA has not been established by medical literature. *Parker,* 2019 WL 3425297, at *25. Petitioner also failed to show that vaccination hastened or worsened RA that was already preclinical (although there as here Dr. Utz contested that the petitioner had preclinical RA). *Id.* at *27. Although Dr. Utz offered a detailed causation theory, he provided no evidence to link this theory to Petitioner's case. *Id.* at 28. Further, evidence shows that Petitioner was susceptible to RA for reasons unrelated to vaccination.[25] *Id.* In terms of onset, Petitioner alleged one day, but later centered on three days. *Id.* The timing proposed by Petitioner's expert was inconsistent and too short to reflect an appropriate temporal relationship for Petitioner's RA to be caused by molecular mimicry. *Id.* at *29.

In *C.P.*, a petitioner alleged that he developed *seronegative* RA as a result of a flu vaccination (with onset two months post-vaccination), but the special master responsible for the case denied entitlement. *C.P.*, 2019 WL 5483621, at *1. Petitioner's theory was that the vaccine acted as the initiating event activating T-lymphocytes and a subsequent immune cascade, which in turn caused recruitment of further immune cells that produce antibodies like the classic RA factor and anti-CCP. *Id.* at *13. However, there is no known cause of seronegative RA, and no known autoantibody associated with the condition. *Id.* at *28. Therefore, though the petitioner's experts provided what was deemed a plausible theory for *seropositive* RA, which has known autoantibodies, the theory did not apply to seronegative RA. *Id.* Further, the petitioner was unable to point to any evidence corroborating the theory that the vaccine caused RA. *Id.* In fact, the record showed that petitioner's initial symptoms may have been distinguishable as due to a preexisting knee injury. *Id.* at *29. Finally, the petitioner's experts placed onset sooner than supported by the record, and petitioner's theory would have required onset within a month, not two as found here. *Id.* at *30.

In *Tullio*, the petitioner alleged that a high-dose flu vaccination caused him to develop RA (with onset approximately one week after vaccination), but the special master responsible for the case also denied entitlement. *Tullio*, 2019 WL 7580149, at *1. There, the special master emphasized that multiple epidemiological studies have not detected an increased incidence of RA after flu vaccination or infection, and that there is ample legal justification for considering

[25] Petitioner's age, race, and gender placed her in a category of individuals with an increased risk for RA. *See Parker*, 2019 WL 3425297, at *28. Petitioner's years of heavy smoking greatly exacerbated that risk and provided an environmental trigger universally accepted in the rheumatological community. *Id.*

epidemiological studies in determining whether the flu vaccine can cause RA. *Id.* at *8. In lieu of epidemiology, the petitioner's experts (one of whom was Dr. Utz again) presented opinions that the flu vaccine can cause RA through the process of molecular mimicry. *Id.* at *12. But proof of mimicry was derived from Blast search evidence of antigen homology, rather than from experimental observation. *Id.* at *14-15. The Blast searches produced far too generalized information and the results did not match the immunologically relevant portions of the flu vaccine. *Id.* at *22. Apart from Blast searches, Dr. Utz based the molecular mimicry theory (where an immune response to a nonself antigen such as components of an influenza vaccine cross reacts with self molecules) on four articles involving hemagglutinin and collagen. *Id.* at *15. However, Dr. Utz failed to provide any basis for evaluating molecular mimicry from the standpoint of bonding between the antigen-presenting cell, and a peptide from the antigen and did not show T cell binding. *Id.* at *16. Additionally, it appeared the petitioner's experts had not personally studied this specific issue themselves. *Id.* at *26.

By contrast, an older case from the Court of Federal Claims, *Campbell*, resulted in a finding that the petitioner had successfully demonstrated that the flu vaccine could cause RA – but it has limited persuasiveness, both regarding the science it relied upon as well as the evidentiary standard it employed. There, an individual received a flu vaccine, and then started to experience limb pain and other symptoms three days later. *Campbell,* 97 Fed. Cl. at 653. The Court overturned the special master's denial of entitlement, finding that a causation theory of molecular mimicry leading to a cross-reaction manifesting as seropositive RA was plausible, and thus (because there was also treater support for the conclusion that the vaccine related to the injury) reliable. *Id.* at 664. This delineation of the *Althen* standard when applied to the first prong, however, flies in the face of determinations by the Federal Circuit in *Boatmon* or *Moberly* that mere plausibility does *not* satisfy reliability or establish preponderance. *Campbell* also does not discuss the epidemiologic evidence undercutting an association between RA and the flu vaccine – evidence that perhaps was not offered in that case, but which *was* offered in *Tullio*, as discussed above.

I have otherwise identified no cases finding that *any* vaccine could cause either the development of rheumatoid factor or the anti-CCP antibodies associated with RA's chronicity. Indeed, given what is known about RA (and in particular the fact that these biomarkers often long precede onset of RA symptoms), it is highly unlikely a vaccine could cause these autoantibodies to spring into being in a medically-reasonable timeframe, such that a vaccine administered close in time to appearance of RA symptoms could be deemed causal. *Olson*, 2017 WL 3624085, at *5.

Reactive arthritis is also a recognized arthritic syndrome, somewhat distinguishable from seropositive RA, and it also has been the subject of prior Program claims. *See,* e.g. *Wyatt v. Sec'y of Health & Human Servs.,* 144 Fed. Cl. 531 (Fed. Cir. 2019); *Campbell v. Sec'y of Health & Human Servs.*, 90 Fed. Cl. 369 (Fed. Cir. 2009). Reactive arthritis is joint pain and swelling triggered by an infection in another part of the body. *Olson,* 2017 WL 3624085, at *n5. (internal quotation marks and citation omitted). Reactive Reiter's syndrome is a type of reactive arthritis where an autoimmune reaction, usually to bacterial infection, occurs. *Dorland's* at 1816; *Gearin*

v. Sec'y of Health & Human Servs., No. 07-0737V, 2008 WL 2009736, at *1-2 (Fed. Cl. Spec. Mstr. January 31, 2008). Some authorities now consider this symptom complex to be more appropriately classified as reactive arthritis and not distinguished or named separately, however. *Id*. Men are most affected by reactive arthritis and it is usually short-lived. *Dorland's* at 154, 1816.

There are few cases discussing how a vaccine could cause reactive arthritis. *See,* e.g., *Suliman v. Sec'y of Health & Human Servs.*, No. 13-993, 2018 WL 6803697, at *30 (Fed. Cl. Spec. Mstr. November 27, 2018); *Frazer v. Sec'y of Health & Human Servs.*, No. 17-1229V, 2019 WL 4741745, at *4 (Fed. Cl. Spec. Mstr. August 9, 2019). Admittedly, the reliability of the association between a vaccine and reactive arthritis is facially greater from the outset, especially when the timeframe is close. *Campbell*, 97 Fed. Cl. at 653. However, this form of arthritis is generally not chronic, and is understood to be a transient infectious reaction – and hence a claim alleging a chronic kind of reactive arthritis is not likely to be able to meet the Act's six-month severity requirement. *Wyatt*, 144 Fed. Cl. at 537-38. And there is no case law discussing how a reactive arthritis triggered by vaccination could transmute into the kind of classic, seropositive RA that Mr. Hock was diagnosed with.

II. *Petitioner Has Not Established that the Flu Vaccine Caused his RA*

This case presents a non-Table, causation-in-fact theory. Thus, although the parties' experts agreed that Petitioner was susceptible to RA, given his family history and smoking background, Petitioner does not maintain that his unmanifested (or, as Dr. Oddis maintained, preclinical) RA was made inevitable or worsened due to vaccination. Similarly, the experts both accepted that Petitioner possessed prior to vaccination important biomarkers (most notably anti-CCP antibodies) strongly associated with seropositive RA – but Dr. Utz did not maintain that the flu vaccine *caused* these autoantibodies to form. Petitioner instead simply argued that the flu vaccine's administration later caused his RA (albeit based upon his personal susceptibility). As a result, I do not analyze Petitioner's success in establishing that the flu vaccine significantly aggravated preclinical, but asymptomatic, RA (although I would not have found significant aggravation was established if he had so argued).[26]

[26] To maintain that a vaccine significantly aggravated a preexisting condition, Petitioner must establish: (1) the person's condition prior to administration of the vaccine, (2) the person's current condition (or the condition following the vaccination if that is also pertinent), (3) whether the person's current condition constitutes a 'significant aggravation' of the person's condition prior to vaccination, (4) a medical theory causally connecting such a significantly worsened condition to the vaccination, (5) a logical sequence of cause and effect showing that the vaccination was the reason for the significant aggravation, and (6) a showing of a proximate temporal relationship between the vaccination and the significant aggravation. *Loving ex rel. Loving v. Sec. of Health & Human Servs.*, 86 Fed. Cl. 135 (Fed. Cir. 2009). Under *Loving* prong 3, Petitioner need not demonstrate an expected outcome and that her current-post vaccination condition was worse than such expected outcome. *Sharpe v. Sec. of Health & Human Servs.*, 964 F.3d 1072, 1081 (Fed. Cir. 2020). Under *Loving* prong 4, Petitioner may make out a prima facie case without eliminating a preexisting condition as the cause of her significantly aggravated injury. *Sharpe,* 964 F.3d at 1083. Petitioner need only present a medically plausible theory demonstrating that a vaccine "can" cause a significant worsening of Petitioner's disorder. *Id*.

A. Petitioner's Causation Theory Has Not Been Reliably Established

In many prior decisions, I have made entitlement determinations based in part on my determination that an expert offered an opinion that exceeded his demonstrated knowledge and experience, or made assertions lacking credibility, or where the expert had a track-record of embracing questionable theories. But Dr. Utz was a credible expert, and he did not engage in the evasions or double-speak that can characterize the testimony of even highly-qualified experts. His reports were substantiated with ample "good science," as Respondent's experts acknowledged. Moreover, many individual elements of his theory were scientifically reliable. This is, therefore, *not* a case where my finding turns on the weight given to expert credibility, comparison of expert credentials, or consideration of an expert's candor in light of past experience in the Program.

However, this case was *also* not a "battle of the experts" in which each side made valid points that must be sifted through and compared – for Petitioner's showing overall was insufficiently persuasive to carry his burden. This is because (as well articulated by the late Dr. Rose) (a) certain "legs" of the immune process Dr. Utz described, while scientifically valid if considered in isolation, were not reliably demonstrated as accurately capturing the flu vaccine's potential role in RA's pathogenesis based on what is known about the disease, and (b) the "handoffs" from one leg of the described immune response to the next were conclusorily-asserted and thinly supported with substantiating proof. I thus reach a conclusion similar to that of the special masters in *Tullio* and *Parker* (both of whom heard similar testimony from Dr. Utz) – that Petitioner's theory lacks sufficient medical or scientific reliability to preponderantly support the conclusion that the flu vaccine "can cause" RA.

Dr. Utz certainly described in good and reliable detail the innate immune system's response to a vaccine. For example, Dr. Utz described how the vaccine triggers the secretion of proinflammatory cytokines capable of causing fever or inflammation. Tr. at 32. He was also accurate in his discussion of the process of "bystander activation" of autoreactive T cells. Third Utz Rep. at 4. As he explained, individuals possess autoreactive T cells capable of recognizing "tens of thousands" of other peptides and are thus potentially cross-reactive (if the recognized peptide is a mimic of a self amino acid sequence). *Id.* And the "third step" of his theory – in which he opined that the adaptive aspect of the immune response triggered by the receipt of the flu vaccine would also play a role in encouraging RA – relied on correct science about the mechanism of molecular mimicry, and the role it is theorized to play in propagating an autoimmune response. Third Utz Rep. at 4; Tr. at 3, 62-63.

In this case, however, Petitioner (1) did not have RA before vaccination, and (2) has not proven that the flu vaccine can transform preclinical RA into manifested RA, for the same reasons discussed herein. As a result, a significant aggravation claim would fail for largely the same reasons that the causation-in-fact claim fails.

However, Dr. Utz did not offer reliable evidence to support his overall contention that each step of the immune process would likely flow into the next, such that the overall reaction to the flu vaccine would become pathologic. Why, for example, would the normal immune response to vaccination turn into one in which autoreactive T cells began to contribute to RA, and if so how? And what evidence is there that RA's pathogenesis is consistent with this bystander activation-driven immune response "handoff"? Dr. Utz's theory cannot fill in this blank, and he did not otherwise show the flu vaccine (or wild flu virus for that matter) is even suspected to cause such a reaction.

The same goes for the transition proposed by Dr. Utz into the third stage, involving the adaptive response (in which T cells or antibodies specific to the flu vaccine's antigens, but mimics of collagen structures, would engage in an autoimmune, cross-reactive attack. Although the way this *might* occur was described plausibly enough, there is an overall dearth of reliable evidence that suggests the flu vaccine or its wild virus (and inherently more immune-triggering) analogue would spark such a process resulting in RA (by, for example, stimulating the production of antigen-specific T cells or antibody-producing B cells) – especially since *other* autoantibodies not considered to be associated with RA are well-understood to propagate the condition.[27] Even if the flu vaccine's antigens did have homology with collagen antigens, why would they *also* upregulate the production of other RA-associated autoantibodies – especially when, as Dr. Utz admitted, they could not explain the presence of those autoantibodies in the first place? The associations Dr. Utz proposed were simply too tenuous, and lacked reliable scientific support tying them together.

Arguments about molecular mimicry were also unpersuasive, no matter how well-accepted the general theory (that *some* autoimmune disease processes are driven by cross-reactions due to mimicry) might be. Thus, Dr. Utz accurately noted that amino acid chains comprising hemagglutinin in the flu virus could be shown to have some sequential or structural identity with collagen, the known antigenic target in RA. Tr. at 36-37, 63-64. But does this establish that the flu virus likely stimulates such a cross reaction – in the absence of experimental evidence exploring the connection, and in the face of evidence (noted by Dr. Rose) of the commonality of molecular mimicry (given the small number of total amino acids that make up proteins in the human body)[28] in nature? Not at all. In this case (as in countless cases before it), a petitioner has once again hoped that recitation of the phrase "molecular mimicry" will help build a preponderant case on the first *Althen* prong, but without offering robust and reliable scientific or medical evidence suggesting that the concept actually bears on the injury and vaccine at issue. *See, Morgan v. Sec. of Health & Human Servs.*, No. 15-1137V, 2019 WL 7498665, at *19 (Fed. Cl. Spec. Mstr. December 4, 2019), *denying review, aff'd*, 148 Fed.Cl. 454 (2020) (holding that for molecular mimicry to have utility

[27] Comparing the impact of intercurrent bacterial infections on RA's pathogenesis to what the flu virus might also accomplish were not persuasive. As Bingham reveals, the connection between the two was evident to researchers based on the fact that "oral conditions" (which would be caused by the bacterial infection) have long been understood to be associated with RA, and because it was thought likely that the bacteria at issue played a role in encouraging the citrullination process that causes the presence of the autoantibodies associated with RA. Bingham at 345-46. The same associations are wholly lacking for the flu virus.

[28] There are only 20 amino acids specified by the genetic code from which proteins are synthesized. *Dorland's* at 60.

as a reliable mechanism, there must be some evidence to support its application to the injury at issue).

Overall, the theory offered in this case presents a clear example of the important legal distinction between *plausible* scientific or medical arguments and *reliable*, persuasive evidence that preponderantly meets the first *Althen* prong. Indeed (and although Dr. Utz reasonably testified that his word usage in his report was not meant to have legal significance), it is somewhat telling that Petitioner's expert so frequently used the word "plausible" in his reports. *See,* e.g., First Utz Rep. at 3, 5, 9, 11, 13, 14, 15, 16, 26, 29, 30.[29] Plausibility merely suggests that an opinion is not "beyond the pale" – that, with some empirical, substantive back-up (whether in the form of experimentation results or other objective findings, direct or indirect) it might well be shown to be scientifically and medically reliable, even if some doubt still existed as to its complete accuracy. It has been noted a thousand times, but I will repeat again: petitioners are not required *ever* in the Vaccine Program to definitively prove that their theory is correct, and thus plausibility is always a reasonable "starting point" for any causal theory.

But (as the Federal Circuit has recognized) plausibility is not a preponderance.[30] And special masters are not called upon merely to determine if a Petitioner has offered *some* evidence – the square peg for the square hole, so to speak – and then find for him if this has occurred. Were that the case, entitlement proceedings would be wholly administrative, rather than the judicial determinations that the Act established. Rather, the process of evaluating a causation theory, as the Federal Circuit has instructed, involves application of the *Daubert* standards of evidentiary reliability, to *weigh* the probative quality of the evidence offered in support of a theory. This weighing goes beyond a judgment of whether the theory "sounds" good, and instead evaluates whether the evidence supporting it exists, or merits the weight urged by the Petitioner. In this case, the theory offered has plausibility – but it *overall* lacks sufficient medical and scientific reliability, thus precluding its acceptance.

B. Petitioner Likely Experienced Vaccine-Induced Symptoms Comparable to Reactive Arthritis - Unrelated to his Development of Seropositive RA

[29] I acknowledge that Dr. Utz *himself* did not merely testify that his theories were plausible, but instead contended that they were preponderantly supported. Tr. at 74, 84. Of course, Program experts do not properly opine on the legal standards used in weighing evidence. Rather, it is for the special master – not a medical expert – to determine if an expert's testimony or evidence preponderantly supports the Petitioner's burden of proof.

[30] The field of cryptozoology (the pseudoscientific study of rumored/mythological animals) provides an admittedly facile yet useful way to illustrate this distinction. A "plausible" case can be made for the conclusion that the Loch Ness Monster exists, based on arguments that a hitherto-unlocated prehistoric remnant fish or mammal is trapped in the deep lake in Scotland, and bulwarked with the numerous eye-witness accounts over the years plus a few grainy photos. Yet it is self-evident that reliable, probative evidence *does not yet exist* to support this contention – and even the most sincere and credentialed expert could not preponderantly establish the creature's existence under the Program's standards based on the existing evidence. While the science supporting vaccine causation is of course far less speculative, the evaluative standards applied to theories lacking reliable preponderant support is the same.

Respondent contends that Petitioner most likely suffers from preclinical RA, a condition that predated his administered flu vaccination on October 20, 2015. Respondent's Pre-Hearing Brief, filed January 23, 2020 (ECF No. 51). Respondent bases this contention on the expertise of Dr. Oddis, who disputed that Petitioner ever "really had a symmetric inflammatory joint – arthropathy" consistent with RA. Tr. at 155. Contrarily, the evidence of joint involvement had greatly diminished over the course of Petitioner's treatment. *Id.* Dr. Oddis did acknowledge the possibility that a flu vaccine could cause transient malaise or pain, but that inflammation associated with it would resolve in short course, and thus not reflect the onset of RA. *Id.* at 140-41.

The medical record suggests that Petitioner had likely suffered a reaction to the flu shot, leading to "an acute onset of reactive arthritis," but that any such initial symptoms appeared to completely resolve as of December 10, 2015. Ex. 3 at 270. Petitioner subsequently experienced some arthritis-like symptoms (such as ankle pain worsened by walking). Ex. 3 at 67-74, 93-98. However, Petitioner was "not demonstrating any inflammatory response" characteristic of true RA despite complaints of ankle pain, and there was no evidence of inflammation biomarkers. Tr. at 116-18; Ex. 3 at 226. The medical records suggest that treaters seemed more focused on treating an infectious process rather than possible RA. Tr. at 118. The medical record also suggests that treaters thought symptoms may be attributable to an "auto -immune reaction" to the flu vaccine, manifesting as serum sickness-related symptoms, although RA was also included in the differential. *Id.* at 204.

Given this record, the Petitioner has not preponderantly established he had RA beginning a day after vaccination. Rather, his symptoms are far more consistent with a transient, reactive arthritis that, even if vaccine-induced, resolved within two months. Dr. Oddis did not dispute the possibility of vaccine involvement in Petitioner's first, arthritis-like symptoms, but maintained that even if this were the case, Petitioner's subsequent course could not also be vaccine-attributed. Tr. at 157. Petitioner's subsequent RA, however, is far more attributable to personal history (both a family history of RA plus a personal history of smoking) plus the RA-associated autoantibodies he was repeatedly shown to possess – independent of the flu vaccine. Petitioner's most recent medical records filed in this case (from 2017) establish that Petitioner still experiences joint pain and is diagnosed with seropositive RA. Ex. 6 at 25. However, Petitioner has not preponderantly established that his reactive arthritis subsequently *became* seropositive RA. At best, it can be concluded from the record that any reaction to the flu vaccine that Petitioner experienced was transient – something the first RA specialist he saw, Dr. Gadzhiev, felt was likely. Ex. 3 at 270.

C. Petitioner did not Preponderantly Establish that Vaccine-caused RA Could Begin or Evolve in the Timeframe in Question

Onset is a significant stumbling block to entitlement in this case – and in fact would defeat the claim even if I accepted Petitioner's causation theory as reliable. This is because the theory ultimately relies on a mechanism inconsistent with the timeframe in which Mr. Hock's symptoms manifested.

Petitioner and his expert do not dispute he first started experiencing symptoms associated with his subsequent RA diagnosis a day after vaccination. This is entirely too fast for a disease process dependent on molecular mimicry to occur – as Dr. Utz admitted. Tr. at 51, 78-79. Nor did Dr. Utz attempt to advance the argument that Petitioner's initial symptoms were unrelated to his RA (such that onset might be later). And in fact Dr. Utz contested that Petitioner had experienced serum sickness, an inherently self-limiting vaccine reaction (which would not otherwise under Petitioner's causation theory lead to RA), although the record far better supports the conclusion that the reactive arthritis-like symptoms that Petitioner first experienced (and which later subsided) were likely better understood to be more like serum sickness than RA.

Petitioner was left with the contention that the innate immune response was sufficient to elicit initial RA symptoms, simply due to the expected immune reaction to vaccination (and in particular to the cytokine production that unquestionably occurs close-in-time to vaccination). But this is where Petitioner's case breaks down considerably. For Petitioner's causation "eggs," so to speak, had already been placed in a basket advocating for the conclusion that the flu vaccine's antigens can produce a cross-reaction via molecular mimicry – a process involving the adaptive response that would not yet begin to occur a day after vaccination.

How, then, would the flu vaccine (in this case, an unadjuvanted version – thus lacking in the vaccine additive used to prompt a more robust immune response – and also not the high dose formulation either) cause this to occur, and in so doing put an admittedly-susceptible person like Mr. Hock on the road to a fully-expressed case of RA? Since there is (as noted above) a dearth of direct evidence associating the vaccine with RA, no matter the mechanism, Petitioner had to propose that the mere immune activation process itself, and its cytokine production, can be pathologic. But – as I have noted repeatedly in other cases – this argument, which attempts to turn on its head what is known about normal vaccine function into a disease process, is not a well-founded or reliable argument supporting vaccine causation. *See,* e.g., *McClellan v. Sec. of Health & Human Servs.*, No. 14-714V, 2019 WL 4072130, at *27 (Fed. Cl. Spec. Mstr. July 23, 2019); *Palattao v. Sec'y of Health & Human Servs.*, No. 13-591V, 2019 WL 989380, at *36 (Fed. Cl. Spec. Mstr. Feb. 4, 2019); *Olson* 2017 WL 3624085, at *20. Petitioner also did not show that cytokine upregulation alone is even associated with RA's pathogenesis – regardless of timeframe. Indeed, cytokine secretion is usually understood to be a time-limited process, so it could only be involved with RA in its earliest stages, given what is known about RA's slow-evolving and insidious nature (at least from the standpoint of clinical manifestations).

The timing of Petitioner's theory is also inconsistent with the record. Petitioner's initial symptoms appeared within one to three days following vaccination. Ex. 2 at 9. Dr. Rose explained that even if memory cells were involved in the pathogenic process, there is insufficient time for the cells to be activated, multiply, produce their effector molecules, and inflict observable clinical injury. Ex. H at 8. Dr. Utz theorized that the vaccine can activate the innate immune system, which in turn produces cytokines, including interferons, which may build up over time and can ultimately

cause disease. Tr. at 77. Bystander activation of autoreactive cells is then triggered by the innate response. *Id.* In a third step, molecular mimicry would take place where autoantibodies produced in response to the vaccine start attacking cells. *Id.* at 78. However, Dr. Utz provided no explanation for the persistence of the upregulation of cytokines, nor did he explain how an innate immune response can lead to chronicity. Dr. Utz admitted that he could find no epidemiologic support for an association between the flu vaccine and RA. *Id*. at 48. The theory simply does not explain why Petitioner would have displayed immediate, RA-like symptoms, then a stuttering course for many months thereafter, in the absence of other corroborative evidence that he was experiencing a persistent inflammatory milieu attributable to a single dose of the flu vaccine.

Thus, Petitioner has not preponderantly demonstrated that the one-day onset of RA-like symptoms he experienced post-vaccination was medically acceptable, since (a) his causation theory proposes a disease mechanism that would likely take longer to unfold, and (b) he did not reliably establish that the flu vaccine could initiate RA via an innate immune response that would later morph into an adaptive, autoimmune-driven response. Rather, the record more preponderantly supports the conclusion that Mr. Hock's RA was in a preclinical stage before vaccination – and that the receipt of the flu vaccine did not hasten or contribute to the manifestation of it, even if it coincidentally caused some non-inflammatory arthralgia-like symptoms that (as Petitioner's rheumatologic treater, Dr. Gadzhiev, surmised) resolved less than two or three months later.

CONCLUSION

It was reasonable for Mr. Hock to suspect that the flu vaccine he had received might have played a role in the sudden manifestation of his joint pain – especially since those symptoms overlapped somewhat with his subsequent medical course, which as it unfolded looked more and more like classic RA. He has also offered a fair expert opinion that is grounded in accurate and reliable science on the specifics. But that theory has not overall been preponderantly established such that I could conclude that the flu vaccine can cause seropositive RA, or did so here. At most, Petitioner's initial symptoms were the transient product of vaccination, but did not initiate a longer disease course, in a person with so many preexisting risk factors and biomarkers.

Accordingly, Petitioner has not carried his burden of proof, and therefore is not entitled to an award of compensation in this case. In the absence of a motion for review filed pursuant to RCFC Appendix B, the clerk of the court **SHALL ENTER JUDGMENT** in accordance with the terms of this decision.[31]

[31] Pursuant to Vaccine Rule 11(a), the parties may expedite entry of judgment if (jointly or separately) they file notices renouncing their right to seek review.

IT IS SO ORDERED.

s/ Brian H. Corcoran
Brian H. Corcoran
Chief Special Master