

In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

DOUGLAS TULLIO,	*	No. 15-51V
	*	Special Master Christian J. Moran
Petitioner,	*	

v.	*	Filed: December 19, 2019
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SECRETARY OF HEALTH	*	Entitlement; flu vaccine; rheumatoid
AND HUMAN SERVICES,	*	arthritis; epidemiology; testability of
	*	molecular mimicry; tetramers
Respondent.	*	

Danielle Anne Strait, Maglio, Christopher & Toale (WA), Seattle, WA, for petitioner;
Lisa Ann Watts, United States Dep’t of Justice, Washington, DC, for respondent.

PUBLISHED DECISION DENYING COMPENSATION¹

Douglas Tullio claims that a flu vaccine he received on September 29, 2012, caused him to develop rheumatoid arthritis (“RA”). He now seeks compensation for his injuries under the Vaccine Act. The Act requires petitioners to provide preponderant evidence that the vaccination caused the injuries they allege before compensation can be awarded. Because the undersigned finds that Mr. Tullio has not met this bar, Mr. Tullio is not entitled to compensation.

¹ Because this decision contains a reasoned explanation for the action in this case, the undersigned is required to post it on the United States Court of Federal Claims' website in accordance with the E-Government Act of 2002. 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services). This means the decision will be available to anyone with access to the internet. In accordance with Vaccine Rule 18(b), the parties have 14 days to identify and move to redact medical or other information, the disclosure of which would constitute an unwarranted invasion of privacy. If, upon review, the undersigned agrees that the identified material fits within this definition, the undersigned will redact such material before posting the decision.

I. Facts

A. **Events in Mr. Tullio's Life**²

Until recently, Mr. Tullio has enjoyed a life of good health. At the time of the vaccination in question, Mr. Tullio was 69 years old and was working nearly full-time as the managing partner of a business owned with his wife. Tr. 13-14. Mr. Tullio describes himself as living an active life and playing golf 2-3 times a week prior to the onset of his rheumatoid arthritis. Tr. 12-13.

Mr. Tullio received a high-dose fluzone influenza vaccine on September 29, 2012. Exhibit 1. Approximately a week after the vaccination, Mr. Tullio began "not moving real well" and began feeling a lot of pain in his lower legs and knees. Tr. 15.

Mr. Tullio saw Dr. John Samples, an internist, twice in October 2012. At the first visit, he complained that his legs had lately "[felt] weaker." Exhibit 16 at 69 (October 12, 2012).³ At the time, Mr. Tullio ascribed the pain to a change in dosage of his heart medication. Id.; see also Tr. 17-20, 35-37, 237, 415-17. Mr. Tullio visited Dr. Samples again 13 days later, on October 25, 2012. This visit was scheduled as a "urgent overbooked visit," with Mr. Tullio complaining of "diffuse body pain" that had been worse since the previous visit. Exhibit 16 at 62; see also Tr. 20-21, 290. Bloodwork found high levels of C-reactive protein ("CRP"), a marker for inflammation. Exhibit 6 at 246; see also Tr. 195, 198, 417-19.

Mr. Tullio continued to complain to multiple providers of pain and weakness in his legs in November and December 2012. Exhibit 16 at 55; exhibit 3 at 20-21, 74; exhibit 4 at 7-9. During these visits, Guillain-Barré syndrome ("GBS") was considered as a possible diagnosis and Mr. Tullio was referred to a neurologist, Dr. Brignoni. Exhibit 11 at 14. Also, during these visits, Mr. Tullio ascribed the onset of his symptoms to his September 29, 2012 flu shot. Exhibit 3 at 7.

² The facts of Mr. Tullio's case are relatively straightforward and not in dispute.

³ The purpose of this visit was to establish care. The note that the visit was to establish care was consistent with Mr. Tullio having recently moved to the Palm Springs area and testimony by Dr. Utz that when a visit to establish care is made, it is often scheduled sooner than other non-urgent visits may otherwise be scheduled. Tr. 235, 288.

On December 4, 2012, he visited with neurologist Dr. Catherine Brignoni. At this visit, he provided a chief complaint of “Possible GBS, diffuse weakness and paresthesia after a flu vaccine.” Exhibit 11 at 14; see also Tr. 23-24. Mr. Tullio had an abnormal neurological exam, with weakness, diminished reflexes, and decreased sensation. Exhibit 11 at 15. Based on those observations and the results of a nerve conduction study (“NCS”), Dr. Brignoni started Mr. Tullio on treatment for GBS and ordered a cerebrospinal fluid (“CSF”) test to assist in the diagnosis.

The results of the CSF test were very abnormal, showing a white blood cell count of 2070 compared to a reference range of 0-5. Based on these results in combination with other testing, Dr. Brignoni diagnosed Mr. Tullio with acute GBS and ascribed the flu vaccine as the cause. Exhibit 16 at 48-51.

From mid-December 2012 to mid-January 2013, Mr. Tullio was treated based on the diagnosis of GBS. However, his treatment was not very effective. Mr. Tullio reported that the plasmapheresis treatments were providing “trace minimal improvement in the pain” and that only epidurals provided relief. Exhibit 16 at 41; see also Tr. 25. Mr. Tullio described at the hearing how the uncertainty regarding his diagnosis and the possibility that he had a proper GBS diagnosis caused him substantial anxiety. Tr. 26.

In light of this uncertainty, Mr. Tullio arranged for a second opinion from UCLA neurology, see Tr. 26, and was seen at UCLA on January 18, 2013, by Dr. Shieh. See exhibit 17 at 10. At this visit, Mr. Tullio’s neurological workup was nearly normal with the exception of his ankle reflexes. Id. at 11. Dr. Shieh concluded that Mr. Tullio’s symptoms were not consistent with GBS and that the CSF analysis was likely spurious. Id.; see also Tr. 314 (indicating the results of the CSF analysis were not consistent with GBS). Dr. Shieh ordered a second CSF test, and indeed the results of this test were normal. At that time, Dr. Shieh recommended that Mr. Tullio see a rheumatologist for further evaluation. Exhibit 17 at 19; see also Tr. 26-27.

Mr. Tullio first saw the rheumatologist, Dr. Sheri Hsu, toward the end of January 2013. Exhibit 4 at 11-15. Dr. Hsu was not immediately able to diagnosis Mr. Tullio’s condition and expressed early concern that Mr. Tullio had a “pain syndrome associated with his flu vaccine.” Id. at 14. Laboratory testing identified elevated CRP and erythrocyte sedimentation rate (“ESR”), but returned normal results for other inflammatory markers including cyclic citrullinated peptides (“CCP”). Exhibit 6 at 20-32. Notably, Mr. Tullio was not suffering from joint swelling (synovitis) at the time of the first visit. Id.; Tr. 27-28. Instead, his symptoms were defined by joint pain (arthralgias).

In February 2013, Mr. Tullio returned to Dr. Hsu, this time complaining of joint swelling. Exhibit 4 at 23. Dr. Hsu now focused on the RA diagnosis. Id.; see also Tr. 419. Further testing showed that Mr. Tullio was responding well to prednisone, a steroid, and methotrexate, an immune system suppressant. Exhibit 10 at 13. He additionally was no longer showing elevated levels of CRP and ESR. Exhibit 6 at 17, 19.

Mr. Tullio continues to see Dr. Hsu to this day. Tr. 28. He reports that his RA is well-managed on various medications. Tr. 29-30. Mr. Tullio reports that he continues to experience pain and swelling in his hands and wrists. Tr. 32. Characteristically, he reports the symptoms are worst in the morning and when he experiences flare-ups. Tr. 33, 40. Otherwise, Mr. Tullio reports that he is doing well and is still able to live an active and fulfilling life. Tr. 40.

B. Mr. Tullio's Illness: Rheumatoid Arthritis

Rheumatoid arthritis is ubiquitous. Its commonness distinguishes it from most injuries that are claimed to be the result of vaccination in this Program. At any given time, RA affects approximately one percent of the population. Exhibit 25 at 7; Tr. 63, 400, 631. However, the lifetime risk of RA is much higher. Approximately 1 in 59 males in the American population will be diagnosed with RA in his lifetime. Tr. 414, relying upon exhibit O (Crowson); Tr. 676.⁴

The underlying cause (or causes) of RA is (or are) unknown. Tr. 68, 219, 285, 401, 406, 508. There are known risk factors for the disease, including age, female sex, genetics, and smoking. Tr. 69. The disease itself presents as an autoimmune reaction wherein the body attacks its own tissue, specifically the synovium—the membrane that lines the body's joints.

The cellular components that are the target for the immune system's attack in RA are thought to be collagen, fibrinogen, enolase, and vimentin. Exhibit 40 at 8 (citing Trouw, exhibit 48); Tr. 94, 365. Each of these proteins is sometimes modified by process known as citrullination. 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). Citrullination is the process of modifying the amino acid arginine to a citrulline. One important feature of this modification is that a class of antibodies, anti-citrullinated protein antibodies (“ACPA”), will attack proteins that

⁴ The bibliographic information for articles this decision cites can be found in the appendix.

have been citrullinated. The presence of ACPA is a key indicator for RA and it marks not only a diagnostic indicator of the disease but is thought to underlie the pathology of the disease as well. When ACPAs are present in the blood of an RA patient, the patients are classified as seropositive RA. Tr. 366, relying upon Trouw.

However, some people with rheumatoid arthritis do not have anti-citrullinated protein antibodies or rheumatoid factor. Tr. 204; exhibit PP, tab 3 (Malmström). These people are classified as having seronegative RA.⁵ Scientists know less about seronegative rheumatoid arthritis because, in part, these patients are rare, making studies about them more difficult. Tr. 64-66, 404.

Regardless of the self-antigen attacked in rheumatoid arthritis, researchers generally believe that T cells damage the synovium. Tr. 95, 105-06, 509. While researchers have not determined why the T cells of some people turn against their host, researchers have discovered that rheumatoid arthritis is more common in people with a set of genes known as HLA-DR4.

The gene HLA-DR4 encodes a series of proteins that comprise part of the major histocompatibility complex, typically abbreviated “MHC.” Tr. 113, 252. MHC is a molecule that is expressed on the outside of an antigen presenting cell, typically abbreviated “APC.” Tr. 111. A purpose of the MHC is to chop a larger antigen into small pieces that it presents to a T cell. Tr. 111, 315. The process of antigen presentation is discussed further in the context of molecular mimicry. See section IV.B, below.

II. Procedural History

Mr. Tullio filed his petition on January 20, 2015. He periodically filed medical records and then filed a statement of completion on April 7, 2015. The Secretary evaluated this evidence and recommended that compensation be denied. Resp’t’s Rep., filed June 17, 2015.

The parties then filed a series of reports from a total of four experts. Mr. Tullio filed the first report, from Paul Utz, on February 29, 2016. Exhibit 25. Mr. Tullio filed supplemental reports from Dr. Utz as exhibit 58 and exhibit 63. These

⁵ Mr. Tullio has seronegative RA. Exhibit 4 at 55 (listing diagnosis as “seronegative RA”); exhibit 10 at 13 (describing Mr. Tullio as a “70 year old male with seronegative arthritis”); exhibit 25 at 6 (“[Mr. Tullio’s] intake diagnosis was listed as ‘seronegative RA.’”); Tr. 67.

supplemental reports primarily responded to opinions that the Secretary's expert, Mehrdad Matloubian, presented in reports filed as exhibits E, PP, and SS.

Although Dr. Utz and Dr. Matloubian served as the primary experts, each party retained a second expert. Mr. Tullio submitted a report from Dr. Steinman as exhibit 40. The Secretary filed reports from Dr. Halsey as exhibits RR and TT.

As the process for obtaining expert reports appeared to be winding down, the parties scheduled the case for a hearing from August 21 to August 23, 2018. In anticipation of the hearing, the undersigned issued an order for submitting more material, including briefs, before the hearing. Order, issued January 26, 2018. The hearing could not happen in August 2018, because an expert developed an unavoidable conflict. See Mot. to Amend Schedule, filed May 9, 2018; order, issued May 14, 2018. The hearing was instead held on March 6-8, 2019, in San Francisco, California.

Before the hearing and in accord with the January 26, 2018 order, Mr. Tullio submitted a brief on January 4, 2019. However, Mr. Tullio's brief did not persuasively advocate his case, and he was instructed to file an amended brief. Order, issued January 22, 2019. Mr. Tullio filed an amended and improved brief on January 28, 2019. The Secretary filed a prehearing brief on February 19, 2019.

In addition to his brief, Mr. Tullio also sought access to the hearing transcript from an assertedly similar case, Parker, No. 14-979V. In Parker, petitioner alleged that the flu vaccine caused rheumatoid arthritis, and the experts were Dr. Utz and Dr. Matloubian. The parties in the present case differed as to whether a special master possessed the authority to order the release of a transcript in one case to a petitioner in another case. See Pet'r's Suppl. Br., filed February 15, 2019; Resp't's Resp., filed February 22, 2019. The parties further argued their positions during the February 25, 2019 pre-trial conference. Ultimately, the undersigned accepted the argument from the Secretary that the Vaccine Act prevented special masters from ordering the release of a transcript to nonparties without the consent of both parties. Order, issued Feb. 26, 2019, at 4, citing 42 U.S.C. § 300aa-12(d)(4)(A).

During the pre-trial conference, the undersigned also consulted the parties about a proposed division of the three days of trial time. The undersigned estimated that approximately 18 hours of testimony time was available and suggested that nine hours should be allotted to Mr. Tullio, six hours allotted to the Secretary, and three hours allotted to the undersigned. The parties agreed to this proposal.

As mentioned above, the hearing took place over three days. All participants complied with the limits on testimonial time. Because the parties had presented their arguments in the brief submitted before the hearing, the parties were not instructed to submit briefs after the hearing. Instead, the case became ready for adjudication upon delivery of the transcript.

III. Standards for Adjudication

A petitioner is required to establish his case by a preponderance of the evidence. 42 U.S.C. § 300aa-13(1)(a). The preponderance of the evidence standard requires a “trier of fact to believe that the existence of a fact is more probable than its nonexistence before [he] may find in favor of the party who has the burden to persuade the judge of the fact's existence.” Moberly v. Sec'y of Health & Human Servs., 592 F.3d 1315, 1322 n.2 (Fed. Cir. 2010) (citations omitted). Proof of medical certainty is not required. Bunting v. Sec'y of Health & Human Servs., 931 F.2d 867, 873 (Fed. Cir. 1991).

Distinguishing between “preponderant evidence” and “medical certainty” is important because a special master should not impose an evidentiary burden that is too high. Andreu v. Sec'y of Health & Human Servs., 569 F.3d 1367, 1379-80 (Fed. Cir. 2009) (reversing special master's decision that petitioners were not entitled to compensation); see also Lampe v. Sec'y of Health & Human Servs., 219 F.3d 1357 (Fed. Cir. 2000); Hodges v. Sec'y of Health & Human Servs., 9 F.3d 958, 961 (Fed. Cir. 1993) (disagreeing with dissenting judge's contention that the special master confused preponderance of the evidence with medical certainty).

Petitioners bear a burden “to show by preponderant evidence that the vaccination brought about [the vaccinee’s] injury by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury.” Althen v. Sec'y of Health & Human Servs., 418 F.3d 1274, 1278 (Fed. Cir. 2005).

In this case, Mr. Tullio’s case largely falls for a failure to present a persuasive medical theory explaining how the flu vaccine “can cause” rheumatoid arthritis. This issue is extensively discussed in section IV, below. The lack of a persuasive theory complicates the analysis of the appropriate temporal relationship, which is prong 3. As explained in section V below, if Mr. Tullio had established that molecular mimicry were a persuasive theory to explain a causal link between flu vaccination and rheumatoid arthritis, then Mr. Tullio would have met his burden regarding timing. But, any gains regarding prong 3 are relatively

inconsequential as Mr. Tullio also has not established, by preponderant evidence, a logical sequence of cause and effect. See section VI, below.

IV. Althen Prong 1: Theory

To restate, a petitioner must establish “a medical theory causally connecting the vaccination and the injury.” Althen, 418 F.3d at 1278. This theory must be persuasive. Boatmon v. Sec’y of Health & Human Servs., 941 F.3d 1351, 1356-57 (Fed. Cir. 2019). In assessing a theory, special masters may look for indicia of reliability. See Moberly, 592 F.3d at 1324.

Evidence relevant to whether the flu vaccine can cause rheumatoid arthritis falls into two broad categories: epidemiological studies and studies relating to the molecular mimicry hypothesis. Due to the strength of the epidemiological studies, these are discussed first in section A. Section B considers the studies the parties put forward regarding molecular mimicry as a mechanistic theory to explain how flu vaccination can cause RA. While sections A and B constitute the bulk of the analysis, the analysis continues for two additional points. Section C highlights the lack of studies directly testing the hypothesis that flu vaccination can cause RA via molecular mimicry. Finally, section D comments upon Dr. Utz and Dr. Steinman as expert witnesses.

A. Epidemiology Exploring Flu Vaccination and Rheumatoid Arthritis

The topic of epidemiology presents two questions. The first is whether special masters in the Vaccine Program should consider epidemiological studies? Because the answer to that question is affirmative as explained in section 1, below, the second question is what have epidemiological studies concerning the association between flu vaccination and rheumatoid arthritis found? As discussed in section 2, multiple epidemiological studies have not detected an increased incidence of rheumatoid arthritis after flu vaccination or flu infection.

1. The Basis for Considering Epidemiological Studies

A lack of epidemiological studies supporting causation does not bar a petitioner from receiving compensation. See Althen, 418 F.3d at 1278 (stating that a petitioner may establish “a persuasive medical theory” through “reputable medical or scientific explanation [,]’ i.e., ‘evidence in the form of scientific studies or expert medical testimony’”) (quoting Grant v. Sec’y of Health & Human Servs., 956 F.2d 1144, 1148 (Fed. Cir. 1992)). However, three reasons support consideration of epidemiological findings when they exist. First and decisively,

the Federal Circuit has endorsed special masters weighing epidemiological studies that investigated whether a vaccination is associated with an increased incidence or worsening of a disease. Second, outside of the Vaccine Program, other legal authorities have also looked at epidemiological studies in analyzing causation questions similar to the causation questions posed in the Vaccine Program. Third, consideration of epidemiological studies is consistent with how researchers and scientists investigate the difficult question of causation.

a) Vaccine Program Precedents Consider Epidemiological Studies

A review of caselaw from the Vaccine Program starts with opinions from the Federal Circuit because opinions from that court establish binding precedent. In a case early in the history of the Vaccine Program, the Federal Circuit determined: “epidemiological studies are probative medical evidence relevant to causation” and “considerable weight [is] due to epidemiological studies in the absence of direct evidence of actual causation.” Grant, 956 F.2d at 1149.

This declaration remains binding because the Federal Circuit has not overturned Grant in an en banc decision. However, a passage from Althen has led to arguments that a consideration of epidemiologic studies implicitly and impermissibly raised the burden of proof. See Althen, 418 F.3d at 1280. Yet, the Federal Circuit has since rejected those arguments albeit in non-binding opinions. See McCollum v. Sec’y of Health & Human Servs., 760 F. App’x 1003, 1009 (Fed. Cir. 2019) (“[T]he special master’s consideration of Duffy [an epidemiologic study] did not amount to a de facto requirement of epidemiological evidence to find this prong met.”); D’Tirole v. Sec’y of Health & Human Servs., 726 F. App’x 809, 811 (Fed. Cir. 2018) (“Nothing in Althen or Capizzano requires the Special Master to ignore probative epidemiological evidence that undermines petitioner’s theory.”).

In addition to Grant, McCollum, and D’Tirole, the Federal Circuit has ruled that special masters may weigh epidemiologic evidence. For example, when determining whether the hepatitis B vaccine can cause multiple sclerosis, the special master in W.C. analyzed three epidemiologic studies involving (a) 643 subjects, (b) 440 case subjects with 950 controls, and (c) 104 subjects in a double-blind placebo-controlled study. W.C. v. Sec’y of Health & Human Servs., No. 07-456V, 2011 WL 4537877, at *14-15 (Fed. Cl. Spec. Mstr. Feb. 22, 2011), mot. for rev. denied, 100 Fed. Cl. 440 (2011), aff’d, 704 F.3d 1352 (Fed. Cir. 2013). The special master found that these studies made the petitioner’s causation theory “extremely unlikely.” Id. at *15. Upon appeal, the Federal Circuit cited those

three studies and ruled that it “cannot say that the special master’s evaluation of the expert testimony or weighing of the scientific evidence was arbitrary or capricious.” W.C. v. Sec’y of Health & Human Servs., 704 F.3d 1352, 1361 (Fed. Cir. 2013).

Finally, the result of many epidemiological studies was one reason, although not necessarily the primary reason, special masters overseeing the Omnibus Autism Proceeding rejected the theory that vaccines can cause autism. See, e.g., Cedillo v. Sec’y of Health & Human Servs., No. 98–916V, 2009 WL 331968, at *84-93 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), mot. for rev. denied, 89 Fed. Cl. 158 (2009), aff’d, 617 F.3d 1328 (Fed. Cir. 2010); Hazlehurst v. Sec’y of Health & Human Servs., No. 03–654V, 2009 WL 332306, at *34–39 (Fed. Cl. Spec. Mstr. Feb. 12, 2009), mot. for rev. denied, 88 Fed. Cl. 473 (2009), aff’d, 604 F.3d 1343 (Fed. Cir. 2010). Thus, special masters’ consideration of epidemiologic studies has a long history that the Federal Circuit has endorsed.

*b) Persuasive Authorities Outside of the Vaccine Program
Consider Epidemiologic Studies*

While much of the procedure in Vaccine Program cases differs from the procedures in traditional litigation, a critical evidentiary question is similar. State and federal courts hear cases in which plaintiffs allege an exposure to a toxic substance caused a harm. The question whether a substance can cause the alleged harm resembles the question in off-Table Vaccine Program cases about whether a vaccine can cause the alleged harm.⁶ The Federal Circuit has recognized this similarity, stating for off-Table cases: “the petitioner is treated as the equivalent of the tort plaintiff and the government is treated as the equivalent of the tort defendant.” Walther v. Sec’y of Health & Human Servs., 485 F.3d 1146, 1151 (Fed. Cir. 2007). Likewise, the Federal Circuit has indicated that causation under general tort law is useful in determining causation for off-Table Vaccine Program claims. See Moberly v. Sec’y of Health & Human Servs., 592 F.3d 1315, 1322-23 (Fed. Cir. 2010); Shyface v. Sec’y, Health & Human Servs., 165 F.3d 1344, 1351 (Fed. Cir. 1999) (“The absence of elaboration of the law of causation in the legislative history leads us to conclude that the Vaccine Act’s requirement of causation in non-Table cases was not viewed as distinct from causation in the tort

⁶ For on-Table cases, the analysis is much different because of the statutory presumption of causation.

law.”). Thus, consideration of how courts have considered epidemiologic studies in analogous settings from tort law is informative.

In cases presenting the question of whether the exposure to some substance has caused an injury, courts have allowed triers of fact to hear evidence based upon epidemiologic studies. For a collection of cases, see David L. Faigan et al., 3 Mod. Sci. Evidence § 23:4. These cases, in turn, are consistent with the guidance of the Federal Judicial Center. The Federal Judicial Center has published a series of guides designed “to assist judges . . . in reaching an informed and reasoned assessment concerning the basis of expert evidence.” Jerome P. Kassirer and Gladys Kessler, Reference Manual on Scientific Evidence, Preface, (3d ed. 2011). According to the Federal Judicial Center, “[e]pidemiologic studies have been well received by courts deciding cases involving toxic substances.” Michael D. Green et al., Reference Manual on Scientific Evidence, Reference Guide on Epidemiology, 549 n.2 (3d ed. 2011) (citing cases). “Epidemiologic evidence identifies agents that are associated with an increased risk of disease in groups of individuals, quantifies the amount of excess disease that is associated with an agent, and provides a profile of the type of individual who is likely to contract a disease after being exposed to an agent.” Id. at 552. The authors of this guide from the Federal Judicial Center emphasize that “an association is not equivalent to causation.” Id. “In evaluating epidemiologic evidence, the key questions, then, are the extent to which a study's limitations compromise its findings and permit inferences about causation.” Id. at 553.

c) Scientists Consider Epidemiology in Deciding Whether a Substance Can Cause an Injury

One factor contributing to the reliability of an expert’s opinion is whether the expert “employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field.” Kumho Tire Co. v. Carmichael, 526 U.S. 137, 152 (1999). Special masters may use this comparison to evaluate opinion evidence presented in the Vaccine Program. Terran v. Sec’y of Health & Human Servs., 195 F.3d 1302, 1316 (Fed. Cir. 1999) (permitting special masters to use Daubert factors); Davis v. Sec’y of Health & Human Servs., 94 Fed. Cl. 53, 66 (2010) (“[U]niquely 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, at least in bench proceedings conducted by special masters in vaccine cases.”), aff’d without op., 420 F. App’x 973 (Fed. Cir. 2011). But see Andreu v. Sec’y of Health & Human Servs., 569 F.3d 1367, 1379 (Fed. Cir. 2009) (“[I]n a field bereft of complete and direct proof

of how vaccines affect the human body,' a paucity of medical literature supporting a particular theory of causation cannot serve as a bar to recovery.") (quoting Althen, 418 F.3d at 1280).

Here, the evidence shows that the medical community relies upon epidemiology. A prominent example comes from Dr. Steinman's experience. By way of background, in 1998, to respond to claims that veterans from the Gulf War incurred various diseases, Congress directed the Secretary of Veterans Affairs to enter into an agreement with the National Academy of Sciences to "evaluate the available scientific evidence regarding associations between illnesses and exposure to toxic agents." Omnibus Consolidated and Emergency Supplemental Appropriations Act, 1999, Public Law 105-277, 112 Stat 2681, Section 1603. Later, Congress further directed the relevant official within the Department of Veterans Affairs to submit a report to Congress about epidemiological research on this topic. Veterans Programs Enhancement Act of 1998, Public Law 105-368, 112 Stat 3315, Section 104. As a member of the National Academy of Sciences, Dr. Steinman reviewed the findings before publication. Exhibit 41 (curriculum vitae) at 3-4; Tr. 381-82. That report begins with an analysis of epidemiology. See exhibit 43 at S-3 through S-7.⁷ Thus, this example demonstrates that the process for determining whether the government should compensate veterans for diseases possibly incurred during their service to their country considered epidemiology.

Like Dr. Steinman, Dr. Utz has used epidemiology in his day-to-day affairs outside of the courtroom. Dr. Utz led the Medical Scientist Training Program at Stanford University for ten years. Exhibit 26 (curriculum vitae) at 2; Tr. 46. In this capacity, Dr. Utz taught students pursuing a joint MD-PhD about the causes of diseases. Dr. Utz testified that he taught students that epidemiology contributes to the analysis of causation. Tr. 246.

A third example of how medical researchers use epidemiology in answering questions about causation comes from Dr. Halsey. Due to his training and experience, Dr. Halsey was recognized as an expert in the fields of vaccines, vaccine safety, and epidemiology. Tr. 567. To assist doctors in determining whether a vaccine adversely affected their patients, Dr. Halsey and colleagues

⁷ Although the researchers from the National Academy of Sciences attempted to use epidemiological studies to determine whether veterans experienced higher incidence of various illnesses, the researchers eventually determined that epidemiological studies were not useful because they lacked a control group.

developed an algorithm, which a peer-reviewed journal published. Exhibit QQ, tab 9 (Halsey), at 5794. In presenting to an audience of medical doctors, Dr. Halsey and colleagues wrote: “Establishing general causation usually requires well-designed epidemiologic studies demonstrating significantly increased risk of the [adverse event] following the vaccine compared with unvaccinated individuals, and/or mechanistic studies such as laboratory investigations implicating the vaccine in affected individuals.” Id. at 5791.

The opinion that Dr. Halsey and colleagues presented here is similar to a statement another researcher expressed. In trying to determine how to consider whether viral vaccines cause autoimmune diseases, Ami Schnatter emphasized the importance of controlled studies of vaccinated and unvaccinated subjects. Exhibit EE (Schattner) at 3881-82; see also Tr. 542 (Dr. Matloubian’s testimony about this article).

Thus, there is ample legal justification for considering epidemiological studies in determining whether the flu vaccine can cause rheumatoid arthritis. Yet, both Dr. Utz and Dr. Steinman opined that epidemiologic studies could provide no information about what happened to Mr. Tullio because Mr. Tullio is a unique or rare case. Dr. Utz disagreed with the idea that there must first be evidence of an epidemiologic association between the vaccine and RA, and stated that “Mr. Tullio unfortunately happens to be a rare person who developed this disorder.” Tr. 243. Similarly, in Dr. Steinman’s view, a study on a population does not say anything when the relevant dataset is composed of one person. Tr. 322.

Such opinions are unpersuasive in light of the existing law reviewed above. According to Dr. Halsey, who possesses greater experience in epidemiology than Dr. Steinman, Mr. Tullio’s uniqueness would not preclude drawing meaningful conclusions from epidemiology. Tr. 600-01. As Dr. Halsey pointed out, epidemiological studies have identified that the risk of developing Guillain-Barré syndrome after flu vaccination is increased by one case or two cases per million doses of vaccination. This example refutes a commonly offered argument that epidemiological studies cannot detect rare events. Id.; see also Tr. 572; exhibit QQ, tab 19 (Salmon). Finally, as discussed at length above, many cases have supported weighing the results of epidemiological studies in determining causation.

2. Epidemiological Studies Investigating a Possible Association between Flu Vaccine and Rheumatoid Arthritis Have Not Detected Any Increased Risk

Through Dr. Halsey and Dr. Matloubian,⁸ the Secretary presented several studies. While the details of the studies are set forth below, the bottom-line conclusion of each study was that researchers did not find a statistically significant increased risk of rheumatoid arthritis among people who received flu vaccine.

a) *Ray*

The subjects of this study were approximately one million members in Kaiser Permanente Northern California from 1997 through 1999. Researchers conducted two types of analyses, a cohort analysis and a case-control analysis. Exhibit CC (Ray) at 6593. In a cohort analysis, individuals who are exposed to a hypothetically causative agent are followed for a period of time to see whether they develop a particular disease and their rate of disease is then compared to controls who did not receive the same allegedly causal agent. See Carda on behalf of G.J.C. v. Sec’y of Health & Human Servs., No. 14-191V, 2017 WL 6887368, at *11 n.13 (Fed. Cl. Spec. Mstr. Nov. 16, 2017) (citing Reference Manual on Scientific Evidence 621 (3rd ed. 2001)); Dwyer v. Sec’y of Health & Human Servs., No. 03-1202V, 2010 WL 892250, at *66 (Fed. Cl. Spec. Mstr. Mar. 12, 2010). In a case-control analysis, researchers examine whether an exposure increased the risk of a disease by looking retrospectively. Mead v. Sec’y of Health & Human Servs., No. 03-215V, 2010 WL 892248, at *37 (Fed. Cl. Spec. Mstr. Mar. 12, 2010).

In Ray, the cohort analysis found a potential increased risk for rheumatoid arthritis in windows approximately six months and one year after flu vaccination.⁹ The relevant portion of table 3 presents this information:

⁸ In general, presentations about epidemiology should come from experts in epidemiology.

⁹ Time periods beyond three months may not be relevant because Dr. Utz testified that a biologically plausible interval between a flu vaccine and the onset of RA was six weeks. Tr. 200; see also Tr. 194 (Dr. Utz: two weeks or three weeks or four weeks is appropriate); Tr. 581 (Dr. Halsey commenting on Dr. Utz’s testimony).

Exposure Interval (days)	Vaccinated Individuals with rheumatoid arthritis (n)	Crude R.R.	Adjusted relative risk	95% CI	p value
90	19	1.19	0.72	0.45, 1.14	0.16
180	62	2.24	1.36	1.03, 1.80	0.03
365	113	2.31	1.34	1.06, 1.69	0.01

The researchers in Ray then conducted a larger case-control study. The case-control study showed that the flu vaccination did not increase the odds ratio in a meaningful way. The relevant portions from table 4 are:

Exposure Interval (days)	Exposed cases, n (%)	Exposed controls, n (%)	Crude O.R.	Adjusted O.R.	95 % CI	p value
90	21 (5.1)	85 (6.8)	0.7	0.7	0.4, 1.2	0.14
180	64 (15.4)	178 (14.3)	1.1	1.1	0.8, 1.6	0.57
365	113 (27.2)	309 (24.8)	1.1	1.1	0.9, 1.5	0.43
730	132 (31.8)	373 (30.0)	1.1	1.1	0.8, 1.4	0.59

The biggest limitation to this study, according to its authors, is that determining the onset of rheumatoid arthritis is difficult. In addition, despite the study's sample size, "if a very small risk of [rheumatoid arthritis] in association with vaccines does exist, a larger study would be needed to detect it." Exhibit CC at 6596.

b) Bengtsson

In this study, these researchers “aimed to elucidate whether common vaccinations given to adults were associated with an increased risk of [rheumatoid arthritis] by using data from a large population-based case-control study on incident cases of [rheumatoid arthritis].” Exhibit A (Bengtsson) at 1831. The researchers used the following methodology. After people were diagnosed with rheumatoid arthritis, researchers gave a questionnaire asking about environmental exposures. The researchers also sent this questionnaire to a group of controls. Overall, researchers identified 2,097 cases and 2,770 controls in total. *Id.* Of this group, 272 cases received the flu vaccine and they were matched with 259 controls. The odds ratio was 1.1 with a 95% confidence interval of 0.9 to 1.3. *Id.* at 1832 (figure 2). According to the authors: “Based on the results of our study which comprised a large number of [rheumatoid arthritis] cases and controls (the study has overall sufficient power (>80%) to detect a RR of 1.19), it is unlikely that vaccinations in general should be considered as a major risk factor for [rheumatoid arthritis].” *Id.* at 1833. According to Dr. Halsey, because the odds ratio was 1.0, there was not even a hint that flu vaccine caused rheumatoid arthritis. Tr. 581.

c) Bardage

These researchers studied 1.98 million people who lived in Stockholm county (Sweden) from January 1, 1998, through at least October 1, 2009. The researchers investigated whether a flu vaccination against H1N1, Pandemrix, affected the risk of neurological and autoimmune disorders. Exhibit QQ, tab 4 (Bardage), at 2. The researchers looked for incidence of diseases within six weeks of the vaccination and determined the hazard ratio under two different models. *Id.* at 3.

For rheumatoid arthritis, table 2 shows:

	Hazard ratio (95% CI)	
	Model 1	Model 2
All vaccinated	1.03 (0.89 to 1.19)	0.94 (0.81 to 1.09)
≤ 45 days	1.17 (0.99 to 1.38)	1.01 (0.86 to 1.20)
> 45 days	0.86 (0.71 to 1.04)	0.84 (0.69 to 1.02)

Based upon these findings, the researchers concluded the risk for rheumatoid arthritis was “unchanged.” Id. at 1.

Each of these three studies found that flu vaccination did not increase the risk of developing rheumatoid arthritis. Dr. Utz and Dr. Steinman acknowledged as much. Tr. 99, 355.

While these studies directly investigated the precise question at hand, other studies investigated a slightly different, but still related, question—whether people who already have rheumatoid arthritis can receive a vaccination effectively and safely? Tr. 420, 587. These studies did not detect any worsening of a person’s rheumatoid arthritis after the person received a flu vaccination. Among these studies, the most meaningful was written by Johanna Westra and others. The Westra authors reported on six studies addressing the safety of flu vaccination in patients with rheumatoid arthritis. They wrote: “In most of the latest studies of the efficacy of influenza vaccination in patients with [rheumatoid arthritis], safety is considered and yet no significant influence of vaccination on disease activity has been reported. Also, in pre-post studies after influenza vaccination, patients with [rheumatoid arthritis] did not experience increased disease activity.”¹⁰ Exhibit II (Westra) at 140; accord Tr. 485 (Dr. Matloubian’s testimony about Westra). As with the studies on whether flu vaccination can cause rheumatoid arthritis, Dr. Utz and Dr. Steinman recognized that flu vaccination is not associated with a worsening of rheumatoid arthritis. Tr. 217 (Dr. Utz); Tr. 364 (Dr. Steinman).

Dr. Halsey testified that a proper conclusion to draw from the epidemiologic studies is the particular study did not detect an increased risk. Tr. 627. If another study were done involving say, ten million people, that larger study may find a risk that smaller studies have not. In other words, epidemiology cannot prove a negative (meaning, epidemiology cannot establish that flu vaccine cannot cause rheumatoid arthritis).

However, the Federal Circuit’s endorsement of special masters’ consideration of epidemiological evidence lends weight to the epidemiological evidence offered here. Of the three most on-point studies, the smallest involved more than two thousand cases of which 257 involved the flu vaccine plus more

¹⁰ Examples of pre and post studies in this record include Saad (exhibit QQ, tab 18) (1,168 patients with RA) and Gabay (exhibit QQ, tab 7). See Tr. 587-92.

than two thousand controls of which 297 matched the flu cases (Bengtsson). The size of Bengtsson is similar in magnitude to the three studies about hepatitis B vaccine and multiple sclerosis that the Federal Circuit reviewed in W.C. (In W.C., the number of participants ranged from 104 subjects to 643 subjects.) But, Bengtsson was the smallest of the three key studies. The other two were larger by orders of magnitude: one million people (Ray) and nearly two million people almost equally divided between subjects and controls (Bardage).

In response to the epidemiology, Dr. Utz and Dr. Steinman had relatively little to say. One of their arguments—that epidemiology is not relevant to individual cases—has been rejected for being inconsistent with both law and medicine. With respect to the specific studies discussed above, Dr. Steinman added a critique that those studies were not relevant to Mr. Tullio’s situation because none of those studies involved the exact vaccine that he received. Tr. 355, 363.

This criticism also misses its mark. The premise of Dr. Steinman’s argument is that flu vaccines differ so greatly from year to year that a study about one flu vaccine cannot be transferred to people receiving a flu vaccine in a different year. Exhibit 40 (Dr. Steinman’s report) at 21. Each flu vaccine protects against three strains of the flu virus and the strains typically change each year.

After Dr. Steinman disclosed this opinion in his report, Dr. Matloubian tested the degree of difference among various iterations of flu vaccines. Using the same methodology Dr. Steinman used to determine the degree of homology between a component of the flu vaccine and a component of joint tissue, which is discussed more extensively below, Dr. Matloubian found that the flu vaccines retain at least 90 percent homology across the years. Exhibit PP (Dr. Matloubian’s report) at 4-7. When asked about this approach, Dr. Steinman did not contest Dr. Matloubian’s findings. Tr. 388-90.

While in this case Dr. Steinman opined that variations in flu vaccinations are so great that one year’s flu vaccine is not relevant to analyzing the effects of another year’s flu vaccine, in another case, Dr. Steinman took the opposite position. There, the vaccinee developed neurologic symptoms within approximately 24 hours of receiving a flu vaccination. To explain how a reaction to the flu vaccination could occur so rapidly, Dr. Steinman relied upon a recall response to a flu vaccine that the vaccinee had received years earlier. So, in that case, the different years’ flu vaccinations were sufficiently similar that one could serve as the recall response for the other. Forrest v. Sec’y of Health & Human

Servs., No. 14-1046V, 2019 WL 925495, at *4, 6 (Fed. Cl. Spec. Mstr. Jan. 28, 2019); see also Tr. 390.

Thus, in this pair of cases, Dr. Steinman's opinion as to whether flu vaccines are similar or are different seemed to shift with the petitioner. When the petitioner's case advanced by having the flu vaccines be similar (Forrest), Dr. Steinman said they are similar. When the petitioner's case is improved by differentiating different years' flu vaccines, as in this case, Dr. Steinman offered an opinion that the flu vaccines are different. Overall, this inconsistency reduces confidence in Dr. Steinman's credibility.

For these reasons, Dr. Steinman's challenge to the usefulness of epidemiologic studies not involving the 2015 flu vaccine that Mr. Tullio received is not persuasive. Instead, the epidemiologic studies are persuasive. As such, the epidemiological evidence weakens the reliability of opinions that the flu vaccine can cause rheumatoid arthritis.

Nevertheless, it remains the case that, as Vaccine Program precedent indicates, epidemiology is not dispositive. See, e.g., McCollum, 760 Fed. App'x at 1009 (noting that a special master may consider epidemiological evidence, but that a claimant need not produce it). Thus, the evidence relevant to Mr. Tullio's hypothesis based upon molecular mimicry is also examined.

B. Molecular Mimicry as a Hypothesis to Explain how the Flu Vaccine Can Cause Rheumatoid Arthritis

In lieu of epidemiology, Mr. Tullio presents the opinions of Dr. Utz and Dr. Steinman that the flu vaccine can cause rheumatoid arthritis through a process known as molecular mimicry. Molecular mimicry is one of the mechanistic theories that petitioners in the Vaccine Program and their experts offer most frequently. See, e.g., Forrest, 2019 WL 925495, at *1; Whelan v. Sec'y of Health & Human Servs., No. 16-1174V, 2019 WL 1061473, at *3 (Fed. Cl. Spec. Mstr. Jan. 28, 2019); B.A. v. Sec'y of Health & Human Servs., No. 11-51V, 2018 WL 6985218, at *1 (Fed. Cl. Spec. Mstr. Dec. 6, 2018); Morgan v. Sec'y of Health & Human Servs., No. 12-77V, 2017 WL 6893079, at *6 (Fed. Cl. Spec. Mstr. Dec. 6, 2017); Smith v. Sec'y of Health & Human Servs., No. 08-864V, 2016 WL 2772194, at *19 (Fed. Cl. Spec. Mstr. April 18, 2016); Perez v. Sec'y of Health & Human Servs., No. 10-659V, 2015 WL 9483680, at *4 (Fed. Cl. Spec. Mstr. Dec. 8, 2015).

The starting point for understanding molecular mimicry is the immune system. In response to encountering a foreign antigen (a vaccine), the body's immune system attempts to neutralize the antigen. This response proceeds through a series of steps involving the innate immune system and (sometimes) the adaptive immune system. The primary actors of the adaptive immune system, which is implicated in the molecular mimicry hypothesis, are T cells and B cells. When the adaptive immune system functions normally, the T cells or B cells proliferate, destroy the antigen, and return to a quiet state. Tr. 76-77.

Unfortunately, in cases of autoimmune diseases, the adaptive immune system goes awry. The body's T cells and/or B cells turn against the constituent host and damage not only the foreign invader but also the body's own tissues. Why autoimmune diseases arise is generally not known. However, molecular mimicry has been suggested to explain the etiology of some autoimmune diseases.

The molecular mimicry hypothesis posits that autoimmune diseases arise when the structure of the foreign invader resembles (or mimics) the structure of cells in the body. This similarity confuses the adaptive immune system and leads antibodies produced by B cells and/or T cells to attack the host, a process sometimes known as "breaking tolerance." In rheumatoid arthritis, the portion of the body that is attacked is the synovium. A constituent part of the synovium is collagen.

This explanation is the foundation for the theory that Dr. Utz and Dr. Steinman offer. Dr. Utz presents a series of articles that, according to him, show that a sufficient degree of similarity between collagen and a portion of the flu vaccine such that T cells attack not only the flu antigens but also collagen. Dr. Steinman supports Dr. Utz's position by providing an opinion about the degree of similarity required to make a cross-reaction possible. On the other hand, Dr. Matloubian disagrees with both Dr. Utz and Dr. Steinman. Dr. Matloubian maintains that the articles on which Dr. Utz has relied do not show similarity between collagen and a portion of the flu vaccine. He also disputes the relevance of Dr. Steinman's opinion.

Weighing the relative persuasiveness of the opinions from experts Mr. Tullio has retained and the expert from the Secretary takes place in the context of how appellate authorities have considered molecular mimicry. These cases are outlined in section 1 below. With this background, the evidence related to molecular mimicry is examined in more detailed in section 2 below.

1. Considerations of Molecular Mimicry by Appellate Authorities in the Vaccine Program

Although special masters have often considered molecular mimicry in their decisions, the number of opinions by appellate authorities on this topic is relatively few. Of this group, the most important is W.C., a precedential opinion from the Federal Circuit.

As discussed in the context of epidemiology, the petitioner in W.C. claimed that the flu vaccine either caused or significantly aggravated his multiple sclerosis. See W.C. v. Sec’y of Health & Human Servs., 704 F.3d 1352 (Fed. Cir. 2016). To support this claim, the petitioner presented an opinion from a neurologist that “through the process of molecular mimicry, the influenza vaccine triggered an immune response which released T-cells that were cross-reactive with myelin. . . . This induced an immune cascade, resulting in inflammation, demyelination, and nerve damage characteristic of multiple sclerosis.” Id. at 1360. According to the Federal Circuit, “The special master found that ‘[m]olecular mimicry is a well-regarded theory in some contexts,’ . . . but correctly required additional evidence showing that molecular mimicry can cause the influenza vaccine to significantly aggravate multiple sclerosis.” Id. (citation omitted).¹¹

The Federal Circuit’s statement that the special master “correctly required additional evidence” concerning molecular mimicry is consistent with the reasoning in Caves v. Sec’y of Health & Human Servs., 100 Fed. Cl. 119 (2011), aff’d without op., 463 F. App’x 932 (Fed. Cir. 2012). In Caves, the petitioner alleged that the flu vaccine caused her to develop transverse myelitis, and she offered the theory of molecular mimicry. Id. at 128. In the underlying decision, the special master found that while “the submitted articles supported the general theory of molecular mimicry . . . the articles do not provide any support for the more specific theory that the influenza vaccine can serve as the antigenic trigger that sets the autoimmune process into motion.” Id. at 129. In resolving a motion

¹¹ There are a handful of examples of established molecular mimicry. See Tr. 607 (Dr. Halsey). Special masters have recognized two examples that do not involve vaccines: rheumatic fever can lead to Sydeham’s chorea, McKown 2019 WL 4072113, at *16; W.C., 2011 WL 4537877, at *11, and *c. jejuni* infection can cause Guillain-Barré syndrome, Isaac v. Sec’y of Health & Human Servs., No. 08-601V, 2012 WL 3609993, at *4 (Fed. Cl. Spec. Mstr. July 30, 2012), mot. for rev. denied, 108 Fed. Cl. 743 (2013), aff’d without op., 540 Fed. App’x 999 (Fed. Cir. 2013).

for review that challenged the special master’s decision, the Court of Federal Claims upheld a method of examination that looks for evidence making the general theory of molecular mimicry a reliable and persuasive explanation for the alleged causal association between the vaccine and disease:

While there is significant support for the general theory, the special master properly concluded that the more specific theory proposed by [the petitioner’s expert] was not supported by any of the evidence presented in this case. . . . The theory of molecular mimicry does not apply specifically to petitioner's case; on the contrary, that general theory could be used to demonstrate an association between virtually any combination of antigens and autoimmune injuries. Without any empirical evidence that the theory actually applies to the influenza vaccine and [transverse myelitis], the first prong of Althen would be rendered meaningless.

Id. at 135.¹²

Thus, according to W.C. and Caves, special masters “correctly” or “properly” look at the evidence underlying the invocation of molecular mimicry. Thus, this decision now turns to the evidence regarding molecular mimicry.

2. Evidence Relating to Molecular Mimicry as a Hypothesis to Explain how the Flu Vaccine Can Cause Rheumatoid Arthritis

Through their experts, the parties submitted a great deal of evidence regarding the reliability of opinions that the flu vaccine can cause rheumatoid arthritis via molecular mimicry. The evidence falls within three broad themes: (a) evidence regarding Blast searches, (b) evidence regarding experiments on the hemagglutinin in flu virus and collagen, and (c) evidence regarding experiments on tetramers.

¹² Caves is not the only decision by the Court of Federal Claims regarding molecular mimicry. However, Caves carries additional persuasive (although still not binding) force because the Federal Circuit affirmed the judgment in Caves pursuant to Rule 36 of the Federal Rules of Appellate Procedure.

a) *Blast Searches*

In his first reports, Dr. Utz proposed that molecular mimicry explains how flu vaccine can cause rheumatoid arthritis. Exhibit 25 at 9-10. After Dr. Matloubian challenged this opinion, exhibit E at 8-13, Mr. Tullio presented a report from Dr. Steinman generally supporting Dr. Utz's opinion. See exhibit 40.

An analysis of Dr. Steinman's opinion entails a further explanation of how T cells respond to antigens. Some antigens, such as those in the flu vaccine, are proteins, and proteins are composed of long strings of amino acids. There are 20 amino acids. When a foreign protein is introduced into the body, a part of the immune system known as an antigen-presenting cell takes up the antigen. The antigen-presenting cell chops up the complete protein into shorter segments, usually comprised of 8-12 amino acids. (This shorter segment is known as a peptide.) As discussed in more detail below, the antigen-presenting cell holds (or binds) the peptide. The T cell, in turn, then sees (or reacts with) the peptide.

As it relates to molecular mimicry, Dr. Steinman's opinion has two parts. First, Dr. Steinman offers an opinion about the degree of similarity necessary to permit a cross-reaction. Second, Dr. Steinman searched a computerized database and found that hemagglutinin and collagen are sufficiently similar.

Based upon experiments in which Dr. Steinman participated, Dr. Steinman opined that in a peptide of 12 amino acids, a cross-reaction can occur when the same amino acid appears in five of the slots. Tr. 332. Dr. Steinman then used this criterion to compare the molecular structures of hemagglutinin and collagen. Tr. 347-53. Despite respondent's opposition, Dr. Steinman's five out of 12 standard is accepted for the sake of argument. But see exhibit QQ (expert report of Dr. Halsey) at 6 (challenging Dr. Steinman's findings); Tr. 612. Thus, the more critical question is whether Dr. Steinman has shown that hemagglutinin and collagen pass this standard.

The second part of Dr. Steinman's work was to review the molecular composition of hemagglutinin and collagen. Dr. Steinman accessed a resource available through the National Institute of Health and entered the relevant proteins. Tr. 388. Through an algorithm, the computer aligns the proteins so that amino acids line up as frequently as possible. Tr. 347-48, 383-85, 388. From this information, Dr. Steinman presented instances in which the homology met or exceeded the 5/12 standard. See exhibit 40 at 7-20.

Dr. Steinman described his work as an “experiment,” Tr. 326, although this term seems to exaggerate his investigation. The database searches seemed to take less than one hour. Tr. 388.

An issue with the theory of molecular mimicry is that because all proteins, which have hundreds of amino acids, are built from the same 20 amino acids, it is inevitable that some sequences of amino acids will repeat. For example, when researchers looked for homology between bacteria and human proteins, they found that at a level of seven amino acids, almost all (99.7%) human proteins overlap with protein sequences found in bacteria. Exhibit TT, tab 6 (Trost); see also Tr. 604. Thus, the finding of sequence homology does not necessarily mean the similarity has significance to the immune system. Tr. 370 (Dr. Steinman), 429 (Dr. Matloubian), 515 (Dr. Matloubian); exhibit SS, tab 2 (IOM report). Dr. Utz, too, questioned the reliance on an approach that involved simply searching for sequence homologies. Tr. 272-73.

Dr. Matloubian, however, did investigate whether the peptides that Dr. Steinman found were biologically relevant. Dr. Matloubian could take this additional step because scientists extensively study the flu virus. In this work, scientists have identified the portions of the flu virus that are peptides and created a database of them. Dr. Matloubian queried the database to see whether the epitopes that Dr. Steinman had identified appeared in the database. Dr. Matloubian disclosed that he did not find any positive hits. Exhibit PP at 3-4, Tr. 483-88, Tr. 545.

When asked about Dr. Matloubian’s methodology of consulting other databases, Dr. Steinman stated that he was aware of databases of known T cell epitopes, Tr. 387, but did not otherwise respond to Dr. Matloubian’s critique of his hypothesis. This lack of meaningful response from Dr. Steinman makes his opinion regarding the usefulness of his Blast searches unpersuasive.

b) T cell Activity in the Molecular Mimicry Context

Apart from Dr. Steinman’s Blast searches, Dr. Utz based his theory of molecular mimicry on four articles reporting on experiments involving hemagglutinin and collagen. See exhibit 25 at 13; exhibit 34 at 8-11; see also Pet’r’s Revised Preh’g Br., filed Jan. 29, 2019, at 15, 17 (identifying these articles). However, before these articles are discussed, it is necessary to refine the meaning of “molecular mimicry.”

At a basic level, molecular mimicry attempts to explain how a T cell can attack both a foreign substance (the hemagglutinin in flu vaccine) and host tissue (the synovium). However, a T cell never sees its target in isolation. A T cell recognizes its target only in the context of an antigen-presenting cell. See Dorland's Illustrated Medical Dictionary 315 (32d ed. 2012) (cell, antigen presenting), 1512 (presentation, antigen). The antigen-presenting cell is like a sausage bun and the peptide is a sausage. Exhibit 34 (Dr. Utz's report) at 9. In the continuation of this simile, the T cell is like mustard or relish that sits on top of the sausage.

This model brings out the fact of two different sets of bonds. The first set of bonds is between the antigen-presenting cell and the peptide. (This is sometimes referred to as bonds on the bottom.) The second set of bonds is between the peptide and the T cell. (This is sometimes referred to as bonds on the top.)

This image helps to visualize the two sets of bonds:

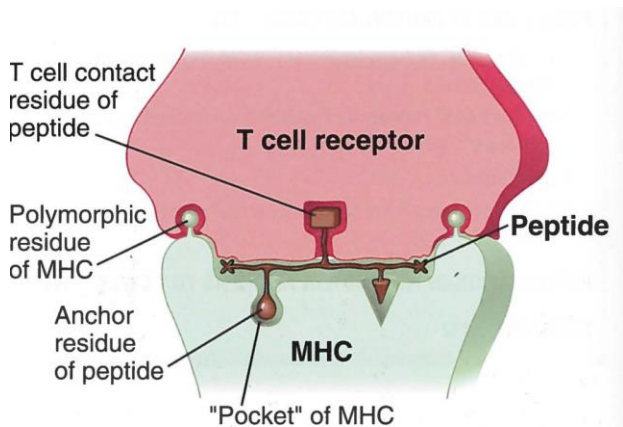


FIGURE 6.1 A model for T cell recognition of a peptide-major histocompatibility complex. This schematic illustration shows an MHC molecule binding and displaying a peptide and a T cell receptor recognizing the complex of peptide and MHC molecule. As discussed later in the text, MHC-associated peptides contain some residues that anchor them into pockets in the cleft of the MHC molecule and other residues that are recognized by T cell antigen receptors. MHC residues that may vary among individuals (polymorphic residues) are also recognized by the T cell receptor. Thus, T cells see both peptide antigens and MHC molecules.

Exhibit SS, tab 1 (Abbas) at 118.

The difference in bonds underlies a dispute between Dr. Utz and Dr. Matloubian about the meaning of molecular mimicry. In his report, Dr. Utz stated that the process of molecular mimicry occurs when “an immune response to a nonself antigen such as components of an influenza vaccine cross reacts with self

molecules.” Exhibit 25 at 9; accord Tr. 124. His later reports and testimony clarified that Dr. Utz included “bottom bonds,” meaning bonds between the antigen-presenting cells and a peptide as fulfilling molecular mimicry.

Dr. Matloubian’s view of molecular mimicry was not as broad. He focused on the T cell (or top) bond:

To an immunologist, [the] definition of molecular mimicry for T cells is that the same T cell (via its unique T cell receptor) can recognize two different antigens (peptides) and become activated by either one of them When two different antigens can be recognized by the same T cell and lead to its activation, they are “molecular mimics” of each other in the immunological sense.

Exhibit SS at 3; accord Tr. 423, 443. Dr. Matloubian’s focus on the T cells is sensible because T cells cause damage in Dr. Utz’s explanation for rheumatoid arthritis. Tr. 222 (Dr. Utz acknowledging T cell activation is part of molecular mimicry), 427 (Dr. Matloubian’s explanation). In an article written for Scientific American, Dr. Steinman illustrated molecular mimicry with a T cell reacting to two antigens. Exhibit 40 at 23; see also Tr. 374-75 (Dr. Steinman testifying about this article), Tr. 425 (Dr. Matloubian stating that his explanation of molecular mimicry “is an agreement . . . with Dr. Steinman’s figure . . . which is in Exhibit 40 on page 23”). Even Dr. Utz agreed that to establish molecular mimicry to a level of scientific certainty, the same T cell must recognize the two different antigens in an antigen-presenting cell. Tr. 162.

However, Dr. Utz’s invocation of the term “scientific certainty” seems to distract from the key issue. Given that the bottom bond is distinct from the top bond, Dr. Utz has not provided any basis for evaluating molecular mimicry from the standpoint of bonding between the antigen-presenting cell and a peptide from the antigen.¹³ While Dr. Utz cited two articles that he claimed supported his definition of molecular mimicry, the relevant passages are written with such generality that they do not inform the question. See Tr. 132-33 (citing exhibit PP, tab 3 (Malmström) at 4-5).

¹³ On a yet even deeper level of immunology, technically the tightness of the bond between the antigen-presenting cell and the antigen affects the way the T cell can bind to the antigen. See Tr. 267-68. However, this nuance does not lead to a different outcome.

With an understanding that molecular mimicry requires the same T cell to see two epitopes on antigen-presenting cells, a detailed discussion of the four articles on which Dr. Utz relies becomes relatively unimportant. Listed in the order of their publication, the four articles are exhibit 39 (Dessen), exhibit 35 (Hennecke and Wiley), exhibit 31 (Sun), and exhibit 37 (Li). Although the science of these articles is complicated, they basically report on how an antigen-presenting cell interacts with hemagglutinin and with collagen. In other words, the articles discuss the bonds on the bottom. The articles do not discuss whether T cells bind to the hemagglutinin and/or collagen as presented through the antigen-presenting cell. For Dessen, see Tr. 227 (Dr. Utz), 453-54 (Dr. Matloubian). For Hennecke and Wiley, see exhibit 34 (Dr. Utz report) at 11 (“this paper only demonstrates that DR4 can bind an influenza or collagen peptide; it does not demonstrate that T cell receptors . . . on human T cells can recognize collagen or influenza peptides), Tr. 228 (Dr. Utz), 454 (Dr. Matloubian). For Sun, see Tr. 156 (Dr. Utz), 522 (Dr. Matloubian referencing Sun). For Li, see Tr. 154-55 (Dr. Utz discussing Li), 463 (Dr. Matloubian discussing Li).

In this context, Dr. Matloubian introduced a new comparison—one with Lego figurines. He said that the bond between the antigen-presenting cell and the antigen’s peptide is like a flat Lego board onto which a set of Lego figurine legs can be placed. Tr. 443. Multiple legs can fit the Lego board. However, the type of legs does not control whether the top part of the Lego figurine is a police officer, a robber, or a stormtrooper. Tr. 443, 466-67. Because the articles on which Dr. Utz was relying do not help with T cell binding on the top of the model, they do not assist in supporting the theory of molecular mimicry.

After Dr. Matloubian had criticized Dr. Utz’s presentation of molecular mimicry without any evidence showing T cell binding, see exhibit E at 12, Dr. Utz took a different tact. In his first report, Dr. Utz had presented a view of how T cells bind to peptides in an antigen presenting cell. Dr. Utz stated: the “T cell repertoire . . . is composed of an estimated $10^{10} - 10^{14}$ different T [cells], each specific for a single epitope.” Exhibit 25 at 9. One T cell sees one epitope. This view appeared to be an orthodox view of immunologists. For example, a widely used textbook for immunology states: “The antigen receptors of $CD4^+$ and $CD8^+$ T cells are specific for peptide antigens that are displayed by MHC molecules (Fig. 6.1) . . . A single T cell can recognize a specific peptide displayed by only one of the large number of different MHC molecules that exist.” Exhibit SS, tab 1 (Abbas) at 118-19.

However, in a supplemental report written in response to an order to disclose all opinions in advance of the hearing, Dr. Utz stated that “It is universally accepted in immunology that T cells do not see one and only one peptide . . . In fact, they almost certainly can recognize tens of thousands of peptides, and likely over a million different peptides.” Exhibit 63 (Dr. Utz report) at 3. The concept that T cells see multiple peptides is called “T cell degeneracy” and “T cell flexibility.” See Tr. 98, 169. In support of T cell degeneracy, Dr. Utz cited three papers—exhibit 68 (Birnbaum), exhibit 69 (Wooldridge), and exhibit 73 (Szomolay).

T cell degeneracy has been mentioned by special masters for more than a decade. See Bubb v. Sec’y of Health & Human Servs., No. 01-721V, 2005 WL 1025707, at *11 (Fed. Cl. Spec. Mstr. April 29, 2005) (summarizing testimony from Dr. Vera Byers and ultimately finding that the petitioner had failed to establish molecular mimicry); see also Garcia v. Sec’y of Health & Human Servs., No. 05-720V, 2008 WL 5068934, at *3 (Fed. Cl. Spec. Mstr. Nov. 12, 2008) (summarizing testimony from Dr. Derek Smith that research in the 1990’s showed that the T cell response is “much more degenerate and less specific than we had previously thought,” and ultimately finding the petitioner was entitled to compensation).

Here, the evidence regarding T cell degeneracy is not robust. The two witnesses who discussed T cell degeneracy are rheumatologists, not immunologists. Although Dr. Utz and Dr. Matloubian possess the background, training, and experience to present opinions about basic immunology, the question of T cell degeneracy would be better informed by a doctor specializing in the more relevant field of immunology. An immunologist would seem better qualified to answer questions about T cell degeneracy, such as, if the research regarding T cell degeneracy had been performed in the 1990’s as Dr. Smith’s testified in Garcia, why does the Abbas textbook still indicate that one T cell recognizes only one peptide on an antigen presenting cell? Under these circumstances, the undersigned is reluctant to accept the reliability of T cell degeneracy. See McKown v. Sec’y of Health & Human Servs., No. 15-1451V, 2019 WL 4072113, at *50 (Fed. Cl. Spec. Mstr. July 15, 2019) (“Dr. Tornatore’s alternative T cell degeneracy mechanism . . . fares no better.”).

Moreover, Mr. Tullio’s attorneys did not integrate the concept of T cell degeneracy with the remainder of his case. The original brief did not cite degeneracy or any of the three relevant articles at all. See Pet’r’s Preh’g Br., filed

Jan. 4, 2019. After being instructed to develop his arguments in more detail, Mr. Tullio's explained why his experts cannot identify the exact self-antigen that caused his rheumatoid arthritis, by citing to the trio of articles. Notably, the Amended Brief did not use the specific term "degeneracy" at all. See Pet'r's Am. Preh'g Br. at 15.

It seems that the T cell degeneracy concept could be useful in the following way. Under the old view, a T cell that recognized and attacked a protein in the synovium, such as collagen, would recognize collagen and only collagen (or something that closely mimicked its molecular structure). Thus, the likelihood of this auto-reactive T cell also recognizing and responding to hemagglutinin would be very unlikely. However, if T cells recognize and respond to millions of proteins because T cells are degenerate, then the likelihood of a cross-reaction to another protein is greatly enhanced.

But, even under the T cell degeneracy concept, it seems that all T cells do not recognize all peptides. Whether any T cell that recognizes a protein associated with rheumatoid arthritis can also recognize hemagglutinin is the next topic.¹⁴

c) Tetramers

Mr. Tullio's last attempt to demonstrate molecular mimicry as a sound and reliable hypothesis to explain how the flu vaccine can cause rheumatoid arthritis is an argument based upon tetramers experiments. This contention lacks persuasive value because Dr. Utz extends the studies beyond what the authors of those studies reported.

Although Dr. Utz eventually came to see tetramers experiments as supporting the molecular mimicry hypothesis, Dr. Matloubian actually introduced a series of articles involving tetramers with his final supplemental report. Exhibit SS. Dr. Matloubian wrote this report in response to Dr. Utz's opinion regarding the testability of molecular mimicry. Dr. Utz had contended that experiments to detect whether a single T cell can bind to both hemagglutination and collagen were expensive and technically challenging. Exhibit 63 at 6. Dr. Utz repeated this

¹⁴ Again, without the benefit of extensive development of the significance of T cell degeneracy from the parties, the undersigned compares the situation to a lottery in which the chances of winning are one in ten billion. Under the old view of a single T cell recognizing a single antigen, a contestant in the lottery received one ticket. Under the T cell degeneracy concept, the contestant receives a million tickets.

opinion in his direct testimony. Tr. 188-89, 214. However, on cross-examination, Dr. Utz seemed to shift, maintaining that articles that Dr. Matloubian had cited to show tetramers experiments undermined molecular mimicry actually showed molecular mimicry in operation. Tr. 240-41; see also Tr. 659-70 (rebuttal testimony). Thus, a more extensive discussion of the tetramers experiments is needed.

In introducing tetramers, Dr. Matloubian stated that tetramers are molecules that “allow identification of T cells that recognize a specific MHC-peptide complex.” Exhibit SS at 11. In this case, the relevant tetramers contain DR4 and are loaded with either hemagglutination or collagen. Id.; Tr. 149 (Dr. Utz); see also Tr. 472-73 (Dr. Matloubian). Using a diagram from the Stanford University medical school website, Dr. Matloubian depicted how tetramers bind to a T-cell receptor:

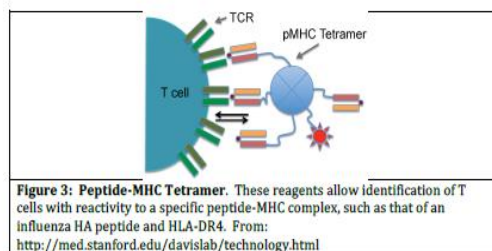


Exhibit SS at 11. This background about tetramers aids in understanding the four papers about tetramers that the parties discussed.

Svendsen. Svendsen was written in 2004, and it appears, at that time, that researchers were struggling to understand the pathology of rheumatoid arthritis. (The pathology of rheumatoid arthritis is still not understood 15 years later.) One issue was whether B cells or T cells initiated the disease. See Exhibit SS, tab 5 (Svendsen) at 7043. The Svendsen group investigated whether collagen-specific T cells contributed to the initiation of rheumatoid arthritis by conducting at least three experiments. Id. Each experiment involved tetramers for collagen and tetramers for hemagglutinin.

In the first experiment, the researchers tested to see whether in a petri dish, tetramers could stimulate T-cell hybridomas specifically. In immunology, “specificity” refers to “the special affinity of antigen for corresponding antibody.” Dorland’s at 1742. The results, presented in figure 1, show that DR4 tetramers for hemagglutinin stimulated T-cell hybridomas for hemagglutinin but not T-cell hybridomas for collagen. Panel a. Similarly, DR4 tetramers for collagen

stimulated T-cell hybridomas for collagen, not T-cell hybridomas for hemagglutinin. Panel b. The authors wrote: “When immobilized on microtiter plates, the homologous, but not the heterologous, DR4 tetramers all stimulated strong dose-dependent responses by the five different hybridomas specific for [hemagglutinin] and the 15 for [collagen].” Exhibit SS, tab 5 (Svendsen) at 7039. The authors added: “The DR4:HA tetramers bound strongly to the five HA(307-319)-specific T-cell hybridomas, but not to any of the [collagen]-specific T cell hybridomas” Id.

In Dr. Matloubian’s view, “none of their HA-specific hybridomas or collagen-specific hybridomas showed cross-reactivity, meaning that they didn’t recognize both collagen and hemagglutinin in the context of HLA-DR4.” Tr. 477; accord Tr. 544-45. Dr. Utz agreed, stating: “[T]hese reagents look very clean. They don’t seem to be cross-reacting for this one T cell receptor” Tr. 661.

The second experiment moves from the petri dish to living mice. Mice genetically modified to develop arthritis were immunized with four substances: collagen, hemagglutinin with a powerful adjuvant, the adjuvant alone, and saline. Thirteen days after vaccination, the researchers obtained blood and the draining lymph nodes from the mice. The researchers then stained with tetramers for either collagen or hemagglutinin. Exhibit SS, tab 5 (Svendsen) at 7040. The researchers determined the frequency of the targeted T cells, expressed as a percentage of T cells.

The results appear in figure 3. When saline was used as the immunizing agent, both collagen and hemagglutinin stimulated no response. The result was 0.00 percent. Panels g and h; see also Tr. 529, 662. When the adjuvant alone was used, the result for collagen was 0.02 percent and the result for hemagglutinin was 0.01 percent. Panels e and f; see also Tr. 662-63.

The controversial part concerns immunization with hemagglutinin and the results that appear in panels k and l. When the lymph nodes were later stained with a hemagglutinin tetramer, the frequency was 0.86 percent. Panel l. The result in panel l is not surprising. However, the arguably surprising result concerns what happened when the lymph nodes, which were from hemagglutinin-immunized mice, were stained with a collagen tetramer—the frequency was 0.08 percent. Panel k.

In Dr. Utz’s view, 0.08 percent is enough to show some cross-reactivity because 0.08 percent is self-evidently greater than zero. He testified that the 0.08 percent result “unequivocally demonstrates if a mouse is immunized with an HA

peptide and then stained with a collagen tetramer, [then] that mouse has cross-reactive T cells between HA and type II collagen.” Tr. 663. However, Dr. Matloubian disagreed. In his view, because of the complexities of working with tetramers and the nature of biologic systems, 0.08 percent was an artifact or background result. Tr. 478-79, 532-34, 553.

On this point, Dr. Matloubian’s opinion is more persuasive.¹⁵ In summarizing the findings of this experiment, the researchers wrote: “Notably, cross-binding of either heterologous tetramer was minimal . . . i.e., not significantly higher than in mice injected with [saline or adjuvant] alone” Exhibit SS, tab 5 (Svendsen) at 7040. Moreover, the “minimal” cross binding shown in figure 3 is consistent with the experiment shown in figure 1. And both figure 1 and figure 3 are consistent with the caption to figure 4.

Figure 4 presents data for another experiment from the Svendsen paper. In this experiment, the researchers extended the duration of the experiment in figure 3, which terminated on day 13, to at least 150 days. The purpose of this experiment was to see how the frequency of collagen-specific T cells correlated to the severity of arthritis in mice. While explaining their data in the caption to figure 4, the researchers wrote: “No DR4:HA(307-319) tetramer staining was detected during the course of the experiments.” Exhibit SS, tab 5 (Svendsen) at 7041. Although Dr. Matloubian mentioned this result in his testimony, Tr. 534, Dr. Utz did not rebut it.

Thus, to summarize Svendsen, in two experiments the data shows no cross-reactivity. Figures 1 and 4. In the third experiment, the degree of cross-reactivity is “minimal” and “not significantly higher” than in controls. Figure 3. Thus, it seems likely that Svendsen undermines the hypothesis that hemagglutinin and collagen can induce the same reaction.

While the parties emphasized Svendsen among all the articles about tetramers, the parties also discussed a few other articles. But, their discussion with respect to these articles was much shorter.

Snir. In 2011, Omri Snir and colleagues, including Vivianne Malmström, continued research into the cause of rheumatoid arthritis. They explored how T cells could attack another protein found in the synovium, called vimentin. Exhibit

¹⁵ Both Dr. Utz and Dr. Matloubian possess a background to opine about tetramers. See Tr. 188 (Dr. Utz), 535 (Dr. Matloubian), 658 (Dr. Utz).

SS, tab 3 (Snir) at 2873. Vimentin can be citrullinated, meaning it can be found in ACPA positive rheumatoid arthritis. Tr. 92.¹⁶

The researchers attempted to determine how modified sequences of amino acids in the citrullinated form of vimentin compared to the unmodified sequence of vimentin. While the specific results do not affect Mr. Tullio's case, the relevant point comes from how the researchers designed their experiment. In the methodology for this experiment, a "hemagglutinin antigen tetramer was used as a negative control." Exhibit SS, tab 3 (Snir) at 2877 (figure 2 legend). Dr. Matloubian interpreted this information as not supporting molecular mimicry. Tr. 482.

Dr. Utz's interpretation, although presented somewhat cursorily, resembled his view of the Svendsen paper. He identified data within figure 3 that showed the percent of T cells responding to hemagglutinin was approximately 0.02 to 0.03 percent. Tr. 241-42; see also Exhibit SS, tab 3 (Snir) at 2878 (figure 3). However, the measured levels are so tiny that, much like the Svendsen group, the Snir researchers used hemagglutinin as a negative control. Apparently, they did not find any response to hemagglutinin meaningful enough to warrant comment.

James. The last experiment involving tetramers for a protein connected to rheumatoid arthritis and hemagglutinin is James.¹⁷ The group of researchers who wrote the James article, published in 2014, included five people who co-authored Snir, including Vivianne Malmström.

The researchers in James roughly followed the same methodology as in Snir. For one experiment involving mice, the James researchers immunized genetically modified mice with vimentin. After 14 days elapsed, the researchers removed the mice's spleens, stimulated the T cells in a petri dish with different substances, and analyzed the results. See Tr. 547 (Dr. Matloubian summary). The researchers were interested in assessing the recall response to "the citrullinated peptide, unmodified peptide, or a control peptide." Exhibit SS, tab 4 (James) at 1715. The control peptide was hemagglutinin. For another experiment, which involved humans, the author stated that using hemagglutinin as a positive control was "important" because the researchers could see whether the changes in T cells were

¹⁶ Mr. Tullio is not ACPA positive.

¹⁷ Dr. Utz also discussed an article by Su, which Dr. Matloubian had submitted originally. Tr. 670-72, 683. However, Dr. Utz's testimony was not persuasive.

due to “[rheumatoid arthritis] itself or to the immunomodulatory therapy that the patients receive.” Id. at 1717.

Malmström. In 2016, Dr. Malmström with Anca I. Catrina and Lars Klareskog, a well-respected rheumatologist, wrote a review article about the etiology of seropositive rheumatoid arthritis. Dr. Utz relied on this article to explain basic concepts in rheumatoid arthritis. Tr. 113-16, 123, 132.

These authors stated that “molecular mimicry” was an attractive hypothesis to explain how the body’s response to an infection of the gums can lead to an attack on yet another protein in the synovium, enolase. Exhibit PP, tab 3 (Malmström) at 4; see also Tr. 131 (Dr. Utz), 514-15 (Dr. Matloubian). In contrast, they described hemagglutinin as “an unrelated antigen.” Exhibit PP, tab 3 (Malmström) at 7, citing Snir and James. The view of these experts that hemagglutinin is “unrelated” to various rheumatoid arthritis associated proteins carries significant weight. See Tr. 411. Furthermore, Dr. Matloubian, in presenting the work of the members of the Malmström and Klareskog group, opined “this is the strongest evidence that there isn’t any [cross-reactivity].” Tr. 551.

When asked about this passage in the Malmström review article, Dr. Utz replied that the Malmström and Klareskog group “are not studying mimicry . . . So they are using this as a control for a totally different purpose.” Tr. 686. This statement seems to confirm that the tetramer articles to which Dr. Utz belatedly turned do not really support the proposition that hemagglutinin and collagen are molecular mimics.

In sum, as discussed in section 1, above, pursuant to W.C., 704 F.3d at 1360, and Caves, 100 Fed. Cl. at 135, petitioners must do more than simply proffer a theory. Petitioners must offer a theory that is “persuasive.” See Boatmon, 941 F.3d at 1356-57.

Overall, the mechanistic evidence fell short of establishing the persuasiveness of molecular mimicry as a theory to explain how flu vaccination can cause rheumatoid arthritis. The Blast searches produced far too generalized information and the results did not match the immunologically relevant portions of the flu vaccine. The studies regarding hemagglutinin and collagen binding to antigen-presenting cells did not show T cell binding. And, lastly, the studies using tetramers tended to show that hemagglutinin and collagen are not molecular mimics.

The mechanistic evidence (section B) tends to align with the epidemiologic evidence, which did not detect an increased incidence of rheumatoid arthritis following flu vaccination (section A). Thus, exclusively for the reasons set forth in sections A and B, Mr. Tullio has failed to carry his burden of presenting a reliable and persuasive theory that the flu vaccine can cause rheumatoid arthritis. This result appears consistent with the outcomes in two leading appellate cases to discuss molecular mimicry, W.C., 704 F.3d at 1360, and Caves, 100 Fed. Cl. at 135, as discussed in section III.B.1, above.

C. Testability

Because the evidence in this case was insufficient to meet the burden regarding a theory, the undersigned discusses what evidence could have been supportive. In doing so, the undersigned recognizes that a petitioner's burden is to present a persuasive theory, not a scientifically certain theory. Bunting v. Sec'y of Health & Human Servs., 931 F.2d 867, 873 (Fed. Cir. 1991). Logically, the following statements can be correct: (1) the evidence in this case did not meet the petitioner's burden to present a persuasive medical theory, (2) some quantum of additional evidence could have been submitted that would have supported a finding that petitioner met his burden, and (3) the quantum of evidence necessary to change from (1) to (2) is less than the quantum of evidence required under a scientific certainty standard. Here, Mr. Tullio could have presented evidence from studies that directly tested the molecular mimicry hypothesis that Dr. Utz and Dr. Steinman have proposed here.

As a matter of law, there seems to be no impediment for considering whether a hypothesis is testable. In guiding trial court judges about the admissibility of expert opinions, the Supreme Court's list of authorized factors begins with testability:

(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 v. Sec'y of Health & Human Servs., 195 F.3d 1302, 1316 n. 2 (Fed. Cir. 1999) (citing Daubert v. Merrell Dow Pharms., Inc., 509 U.S. 579, 592-95 (1993)). Special masters may use the Daubert factors in evaluating the persuasiveness of expert testimony. Terran, 195 F.3d at 1316.

Outside of litigation, testing of hypotheses places a critical role. Although Henry Petroski was writing in the context of engineering, his comments describe a process different disciplines use to advance knowledge.¹⁸ Petroski begins by explaining how a theory is created:

The object of a science may be said to be to construct theories about the behavior of whatever it is that the science studies. Observation and experience, inspiration and serendity, genius and just good guesses—by their presence and absence, in pinches and dashes—all can provide the recipe for a scientific theory. As with all recipes, in which the cook is always the invisible ingredient, the individuality of the scientist provides the inexpressible human flavor. This aspect of science, the concoction of theories, has no universal method.

Henry Petroski, To Engineer is Human: The Role of Failure in Successful Design 42 (1985). Petroski then describes the next step in the scientific process:

But once a theory has evolved, perhaps from a half-baked idea to a precise and unambiguous statement of the scientist's entry in the great universal cook-off, the scientific method may be used to judge the success or failure of a given theory or the relative merits of competing theories. Theories entered in the scientific cooking contest are known as hypotheses and the process of judging is known as the testing of hypotheses.

Id. Daubert's endorsement of the testability of a theory seems to ratify the scientific method Petroski captured. Because the legal foundation for considering the testability of a hypothesis seems established, the next question is whether the evidence in this case shows that the proposed hypothesis—that hemagglutinin and collagen are molecular mimics—can be tested.

In this case, the evidence shows that researchers in laboratories have tested the hypothesis that molecular mimicry plays a role in the pathogenesis of rheumatoid arthritis. For example, in a review article about “research related to the

¹⁸ Petroski wrote the “Reference Guide on Engineering Practice and Methods” in the 2000 edition of the Federal Judicial Center’s Reference Manual on Scientific Evidence.

associations between periodontal disease and rheumatoid arthritis,” the authors, Clifton O. Bingham III and Malini Moni, described a study from 2011 by AJ Kinloch and others.¹⁹ Exhibit 36 (Bingham) at 7. According to Bingham and Moni, Kinloch tested whether peptides from the bacteria that cause gum infections (*Porphyromonas gingivalis*) could participate in the development of arthritis. The Kinloch group found supporting evidence. *Id.* at 7.²⁰ Other support for the molecular mimicry hypothesis as a link between *P. gingivalis* and enolase is found in Lundberg. Exhibit 38 (Lundberg) at 2; see also Tr. 435 (Dr. Matloubian). When asked whether these experiments could be done after substituting hemagglutinin for *P. gingivalis*, Dr. Utz said the experiments could be done. Tr. 263. When asked whether the experiments *had been* done, Dr. Utz said he was not aware of any. Tr. 265.²¹

Another example of testing molecular mimicry in the context of rheumatoid arthritis comes from an older experiment. In 1998, researchers attempted to determine whether a portion of the Epstein-Barr virus was similar to collagen by testing the sera of patients with rheumatoid arthritis. They concluded: “Evidence for molecular mimicry was not found.” Exhibit Y (Davies) at 53. When asked about using the methodology in this paper to test hemagglutinin rather than Epstein-Barr virus, Dr. Utz had difficulty answering the question initially. However, he ultimately responded that the experiment would be difficult to perform because hemagglutinin is a more challenging protein due to its “sugar residues.” Tr. 261.

Dr. Steinman was direct in stating that molecular mimicry can be tested. Tr. 321-22; but see Tr. 385-86. He said that hemagglutinin could be put into genetically engineered mice to see whether the animals developed rheumatoid arthritis. Tr. 324, 334. On cross-examination, Dr. Steinman was asked whether he could submit his theory for peer review. In answering, Dr. Steinman said: “I might try to do the experiment[:] inducing disease in a humanized mouse with those

¹⁹ The underlying article by Kinloch is not part of this record.

²⁰ The 2017 Malmström article states epidemiological data has not shown a clear relationship between periodontitis and rheumatoid arthritis. Exhibit PP, tab 3 (Malmström) at 4-5.

²¹ Later, in rebuttal testimony, Dr. Utz pointed to the tetramers experience, including Svendsen, as experiments involving hemagglutinin that support cross-reactivity with collagen. However, for the reasons explained above, Dr. Utz's opinion about the tetramers studies was not persuasive.

peptides.” Tr. 373. His answer here may reflect his earlier testimony on direct examination that he is “not applying for a prize,” suggesting that his methods in forming an opinion in a legal proceeding are less stringent than if he were submitting his theory for peer review. Tr. 354. For example, when asked on cross-examination about submitting his database search to a journal that publishes peer-reviewed articles, Dr. Steinman stated that his work is sufficient for a court but not for the broader community. Tr. 354 (“And that’s about the best I could do and that’s the foundation of a theory for this Court. I’m not applying for a prize. I’m just saying that this is where an experiment led me . . .”). Dr. Steinman also stated that if he were trying to publish a paper in a peer-reviewed journal, he would do more, such as model his theory in mice. Tr. 373.

In short, Dr. Utz and Dr. Steinman have presented a hypothesis—hemagglutinin and collagen are molecular mimics—that is testable, but has not been tested directly. Why does this gap of knowledge and evidence exist? Potentially contributing factors stem from the scientific and legal communities.

Regarding the scientific community, Dr. Matloubian stated that he analyzed the evidence in the same way he approaches reviewing an application for a grant. Tr. 432. Grant approval would be one practical way to fund an experiment. See Tr. 373-74. However, according to Dr. Matloubian, people would determine whether to fund the research after considering, among other factors, the data that do and do not support the hypothesis. Tr. 432. The fact that epidemiology has not detected a statistically significant increase in rheumatoid arthritis after flu vaccination (or flu infection) and the fact that hemagglutinin is used as a control in experiments testing reactivity of RA-proteins suggest that the medical community would not want to devote scarce research dollars into investigating this hypothesis. Tr. 606-09 (Dr. Halsey).

Regardless of the motivations of the broader medical and/or scientific communities, the parties in this legal proceeding could have some interest in testing the molecular mimicry hypothesis. See Sanne H. Knudsen, Adversarial Science, 100 Iowa L. Rev. 1503 (2015); Samuel L. Tarry, Jr., Can Litigation-Generated Science Promote Public Health?, 33 Am. J. Trial Advoc. 315 (2009); William L. Anderson et al., Daubert’s Backwash: Litigation-Generated Science, 34 U. Mich. J.L. Reform 619 (2001). Although not a party-litigant, Dr. Utz expressed frustration about resistance to acceptance of molecular mimicry as a theory. Tr.

253.²² Dr. Utz’s dismay, in turn, seems to stem from a belief that he has done all that is possible, except for conducting an unethical experiment to produce rheumatoid arthritis in a healthy person. Exhibit 58 (Dr. Utz’s third report) at 4. But, Dr. Utz seemed to overlook an intermediate step – mouse models. Tr. 269.

For rheumatoid arthritis, research by Svendsen, Snir, James, and Kinloch suggest that one step would be to model people’s response to a vaccine with an animal. The animal model would be a chance to examine whether a living organism reacted in a way the molecular mimicry hypothesis predicts. See Tr. 273 (Dr. Utz’s testimony recommending studies involving living T cells); see also Tr. 270 (remarking about the Sun paper, “it is curious to me that they would, in fact, go from a human experiment . . . backwards into a mouse experiment . . . [I]f one were to do mouse experiments, they could look more at the mechanism where it might work where the different cells might go, those sorts of things.”).

Dr. Steinman recognized that “[e]xperiments can settle the disagreement,” Tr. 321, and that he could perform the perfect experiment in a mouse model. Tr. 334. But, in Dr. Steinman’s words, he did not have this responsibility when presenting materials for a court. See Tr. 373; see also Tr. 334 (“[M]y job is to make a theory, not to do the perfectly relevant experiment.”). With incentives from the legal system, one party or both parties could investigate the persuasiveness of molecular mimicry as a hypothesis to explain how a vaccine can cause a disease. Of course, any study would require both time and resources.²³

If Dr. Steinman or Dr. Utz had conducted experiments about molecular mimicry, the results could have assisted Mr. Tullio in meeting his burden of proof. Cf. Libas v. United States, 193 F.3d 1361, 1365-69 (Fed. Cir. 1999) (vacating factual finding of the Court of International Trade that a certain fabric was powerloomed because the record did not support the reliability of the test used to

²² In this context, Dr. Utz compares the process of determining a cause for rheumatoid arthritis to the process of diagnosing and treating a patient with rheumatoid arthritis. This comparison seems inapt as the patient might benefit from an unproven treatment that carries little risk.

²³ The Vaccine Program would seem to allow for time to seek approval from an overseeing institution, to carry out the experiment, and to submit an article for peer review because the pace of litigation has dramatically slowed. Mr. Tullio’s case came to hearing approximately four years after it was filed and this time was relatively quick. Moreover, the presence of approximately \$4 billion in the Vaccine Injury Compensation Trust Fund suggests that money is available to pay for experiments.

distinguish hand-loomed and power-loomed fabrics); Pride v. BIC Corp., 218 F.3d 566, 578 (6th Cir. 2000) (“The failure of [the plaintiff’s] experts to test their hypotheses in a timely and reliable manner or to validate their hypotheses by reference to generally accepted scientific principles as applied to the facts of this case renders their testimony on the cause and origin of the fire unreliable . . .”).²⁴

Testing the hypothesis could lead to information relevant to the other Daubert factors. The results of an experiment using an animal model could, in turn, be written in an article submitted for peer review. (Peer review is the second Daubert factor.) When Dr. Utz presented his opinions at the hearing, he had not written any articles proposing that the flu vaccine can cause rheumatoid arthritis. Tr. 217-18. Likewise, Dr. Utz had not presented the hypothesis that flu vaccine can cause rheumatoid arthritis to a national meeting. Tr. 219. Without this foundational work, the specific theory does not enjoy general acceptance in the medical community. Cf. Tr. 217 (Dr. Utz stating that none of the literature identifies flu infection as a possible cause for rheumatoid arthritis), 363 (similar testimony from Dr. Steinman). (General acceptance is the fourth Daubert factor.) Thus, an experiment involving an animal model could advance a petitioner’s attempt to satisfy the various Daubert factors.

In saying Mr. Tullio and his experts could have presented more evidence, the undersigned might be perceived as demanding proof beyond a reasonable doubt. The undersigned is aware that the standard is simple preponderance. See Hodges v. Sec’y of Health & Human Servs., 9 F.3d 958, 961-62 (Fed. Cir. 1993) (disagreeing with a dissent that opined the special master had imposed too high a standard). But, even under the preponderance of evidence standard, a theory must be “sound and reliable.” Boatmon, 941 F.3d at 1359 (quoting Knudsen v. Sec’y of Health & Human Servs., 35 F.3d 543, 548-49 (Fed. Cir. 1994)). As discussed in sections A and B, the epidemiology and the mechanistic evidence do not support a finding that the hypothesis of molecular mimicry between flu vaccine and hemagglutinin is sound and reliable. Therefore, the lack of testing does not affect

²⁴ Alternatively, special masters could expect that experts the Secretary retained (here, Dr. Matloubian and Dr. Halsey) would experiment to test the hypothesis that petitioner’s experts proposed. Some cases seem to place the burden of testing on the party opposing the proposed theory. “Testability ‘assures the opponent of proffered evidence the possibility of meaningful cross-examination (should he or someone else undertake the testing).’” City of Pomona v. SQM North America Corp., 750 F.3d 1036, 1046 (9th Cir. 2014) (quoting United States v. Mitchell, 365 F.3d 215, 238 (3d Cir. 2004)) (reversing the district court’s exclusion of expert opinion based on an erroneous application of the Daubert “testability” prong).

the outcome of the case—if this section on testability were excised from the decision, the undersigned still would have found that Mr. Tullio did not establish prong 1.

D. Dr. Utz and Dr. Steinman as Experts

Lastly, a finding that the opinions of Dr. Utz and Dr. Steinman are not persuasive in this case should not be construed as findings about Dr. Utz and Dr. Steinman themselves. Both have accomplished much in their careers. They have directly cared for patients and trained other medical professionals who have gone on to care for other patients. They have researched treatments that have helped countless people. Indeed, their professional achievements show that more is possible in their work as experts.

If there is a flaw in Dr. Steinman’s presentation as an expert in this case, it is that Dr. Steinman seemed to indicate that he expressed opinions, as an expert, more readily than he would outside a legal proceeding. Tr. 373-74. Other special masters have expressed similar concerns. See D.G. v. Sec’y of Health & Human Servs., No. 11-577V, 2019 WL 2511769, at *182 (Fed. Cl. Spec. Mstr. May 24, 2019) (Dr. Steinman “flits back and forth from opinion to opinion to assist petitioner in prevailing, even if he does not eventually believe what he wrote or said. Dr. Steinman is the essence of a team player, in other words, an advocate.”); China v. Sec’y of Health & Human Servs., No. 15-095V, 2019 WL 1873322, at *19 (Fed. Cl. Spec. Mstr. Mar. 15, 2019), mot. for rev. denied, 144 Fed. Cl. 378, 386-87 (2019). This dichotomy is inconsistent with the purpose of Daubert test as “mak[ing] certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field.” Kumho Tire, 526 U.S. at 152 (1999). It also appears that when Dr. Steinman is appearing in a courtroom on behalf of Mr. Tullio, he is disclaiming a methodology (epidemiology) that he supported when he was participating in the report for the Persian Gulf veterans. See Tr. 381-83; see also exhibit 41 at 3-4; exhibit 43, tabs 1-3. However, Dr. Steinman’s approach might be consistent with a view that distinguishes scientists from participants in the civil litigation. See Andreu, 569 F.3d at 1380 (“Medical literature and epidemiological evidence must be viewed, however, not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act’s preponderant evidence standard . . .”).

To the extent that Dr. Steinman shaped his opinions due to the litigation setting, the undersigned did not detect that Dr. Steinman was motivated because he was being paid for his time. Dr. Utz and Dr. Steinman testified that they earn

money outside the Vaccine Program, including work as experts. Tr. 53-58 (Dr. Utz), 307 (Dr. Steinman), 359-61 (Dr. Steinman). This information suggested that compensation through the Vaccine Program is less than the amounts received elsewhere.²⁵ While Dr. Steinman receives monetary compensation, he also stated that participating in the Vaccine Program keeps him “sharp” thinking about “fascinating” cases. Tr. 308; accord Tr. 357. It seems that these non-pecuniary benefits also motivate Dr. Steinman’s participation in the Vaccine Program.

Regardless, this case does not turn on why experts presented the opinions they presented. Instead, the case resolves on the (lack of) persuasiveness of the theory that the flu vaccine can cause rheumatoid arthritis via molecular mimicry. As discussed above, the powerful epidemiologic evidence does not support this hypothesis. Dr. Matloubian easily refuted the usefulness of Dr. Steinman’s Blast searches. Finally, the complicated tetramer studies contradict, rather than support, the assertion that hemagglutinin mimics collagen in an immunologically meaningful way. Consequently, Mr. Tullio did not meet his burden of proof for Althen prong one. While the finding on prong one means that Mr. Tullio is not entitled to compensation, the remaining two Althen prongs are reviewed for completeness.

V. Althen Prong 3: Timing

The timing prong from Althen actually contains two parts. A petitioner must show the “timeframe for which it is medically acceptable to infer causation” and that the onset of the disease occurred in this period. Shapiro v. Sec’y of Health & Human Servs., 101 Fed. Cl. 532, 542-43 (2011), recons. denied after remand on other grounds, 105 Fed. Cl. 353 (2012), aff’d without op., 503 F. App’x 952 (Fed. Cir. 2013).

A. Appropriate Temporal Interval

As discussed in section III.B above, Mr. Tullio and his experts advance the theory of molecular mimicry. Dr. Utz explained that molecular mimicry would not

²⁵ Although Dr. Utz and Dr. Steinman could earn more money working outside of the Vaccine Program, Dr. Utz and Dr. Steinman receive compensation at a higher hourly rate than Dr. Matloubian and Dr. Halsey. The hourly rates for Dr. Matloubian and Dr. Halsey are \$300 per hour for most activities and \$150 per hour for travel. Tr. 399, 497-98, 566. Furthermore, the higher hourly rates for the petitioner's expert more than offset the delay in payment that the petitioner's experts encounter.

occur immediately because the immune system must ramp up before the immune system would damage host cells. Tr. 193. Although Dr. Utz's testimony was not as clear as possible on this point, he seemed to indicate that the process of molecular mimicry would take at least one week. Tr. 159, 193, 211.

As discussed above, Dr. Matloubian disagrees with the premise that molecular mimicry can explain a relationship between flu vaccine and rheumatoid arthritis. Dr. Matloubian pointed out that rheumatoid arthritis is not usually considered a post-infectious disease and the triggers for the disease are not known. Tr. 402, 407. One of the proposed triggers, smoking, could expose a person to developing rheumatoid arthritis for years before the autoimmune attack on joints begins. Tr. 407. Thus, to Dr. Matloubian, attempting to determine the appropriate interval for an inference of causation is a non-sequitur because the pathogenesis of rheumatoid arthritis is not known.

When asked about molecular mimicry more generally, Dr. Matloubian stated that the process of molecular mimicry would take at least one week to begin. Tr. 431, 512. Dr. Matloubian also set an outer bound for the occurrence of molecular mimicry at six weeks. Id.

If Mr. Tullio had established the persuasiveness of the molecular mimicry theory to explain how flu vaccine can cause rheumatoid arthritis, then the appropriate time period would be one to six weeks.

B. Onset of Mr. Tullio's Rheumatoid Arthritis

Mr. Tullio received the flu vaccine on September 20, 2012. Exhibit 1. According to his testimony, he began to experience pain in his legs, especially his calves, about one week later. Tr. 15. Dr. Utz saw this calf pain as an unusual manifestation of rheumatoid arthritis. Tr. 71, 192-93, 235.

Dr. Matloubian placed the onset of Mr. Tullio's rheumatoid arthritis at about a month later, on October 25, 2012. Tr. 512. On this date, Mr. Tullio complained to Dr. Samples about "diffuse body pain," exhibit 16 at 62, and lab work uncovered high levels of C-reactive protein, exhibit 6 at 246.

Whether Mr. Tullio's rheumatoid arthritis started on September 27, 2012, or October 25, 2012, is not material. Both dates fit within the accepted temporal interval of one to six weeks. Therefore, if Mr. Tullio had established prong one, he would have also established prong three.

VI. Althen Prong 2: Logical Sequence of Cause and Effect

The final prong from Althen is for a petitioner to demonstrate “a logical sequence of cause and effect.” 418 F.3d at 1278. The Federal Circuit has encouraged special masters to consider carefully the views of any treating doctor.

Here, no treating doctor has persuasively opined that the flu vaccination caused Mr. Tullio’s rheumatoid arthritis. See Pet’r’s Am. Preh’g Br. at 20. The potentially most supportive statement came from Dr. Hsu, who diagnosed Mr. Tullio with rheumatoid arthritis and who has treated him. Relatively early in her treatment of him, Dr. Hsu stated: “I am concerned about a pain syndrome associated with his flu vaccine.” Exhibit 4 at 14 (report dated Jan. 30, 2013). However, as the Secretary notes, Resp’t’s Preh’g Br. at 22, after Dr. Hsu diagnosed Mr. Tullio with rheumatoid arthritis, she did not associate his disease with his flu vaccination.

The lack of support from treating doctors is consistent with the lack of information about the cause of rheumatoid arthritis. As explained much earlier in section I.B of this decision, the cause of rheumatoid arthritis is not known. Furthermore, when epidemiologic studies have explored a potential association, they have not found an increased incidence of rheumatoid arthritis in people who received the flu vaccine. Thus, given this information, it would be surprising for a doctor to tell Mr. Tullio that the flu vaccination caused his rheumatoid arthritis. See Tr. 219 (Dr. Utz stating that he has never told any of his rheumatoid arthritis patients that flu vaccination caused their rheumatoid arthritis).

VII. Conclusion

For the foregoing reasons, Mr. Tullio has not presented sufficient evidence to show that the flu vaccine caused him to develop rheumatoid arthritis. Accordingly, his claim for compensation is DENIED.

The Clerk’s Office is instructed to enter judgment in accord with this decision.

IT IS SO ORDERED.

s/ Christian J. Moran
Christian J. Moran
Special Master

Appendix of Articles Cited

- A.K. Abbas et al., *Antigen Presentation to T Lymphocytes and the Functions of Major Histocompatibility Complex Molecules*, in Cellular and Molecular Immunology 117 (2017), filed as exhibit SS, tab 1.
- Carola Bardage et al., *Neurological and autoimmune disorders after vaccination against pandemic influenza A (H1N1) with a monovalent adjuvanted vaccine: population based cohort study in Stockholm, Sweden*, 343 BMJ d5956 (2011), filed as exhibit QQ, tab 4.
- Camilla Bengtsson et al., *Common vaccinations among adults do not increase the risk of developing rheumatoid arthritis: results from the Swedish EIRA study*, 69 Annals of the Rheumatic Diseases 1831 (2010), filed as exhibit A.
- Clifton O. Bingham III & Malini Moni, *Periodontal disease and rheumatoid arthritis: the evidence accumulates for complex pathobiologic interactions*, 25 Current Opinion in Rheumatology 345 (2013), filed as exhibit 36.
- Michael E. Birnbaum et al., *Deconstructing the peptide-MHC specificity of T cell recognition*, 157 Cell 1073 (2014), filed as exhibit 68.
- Deborah Cory-Slechta & Robert Wedge (editors), *Committee on Gulf War and Health Volume 10: Update of Health Effects of Serving in the Gulf War*, 10 Gulf War Health S-1 (2016), filed as exhibit 43.
- Cynthia C. Crowson et al., *The Lifetime Risk of Adult-Onset Rheumatoid Arthritis and Other Inflammatory Autoimmune Rheumatic Diseases*, 63 Arthritis & Rheumatism 633 (2011), filed as exhibit O.
- J.M. Davies et al., *Rheumatoid Arthritis Sera React with a Phage-Displayed Peptide Selected by a Monoclonal Antibody to Type II Collagen that has Homology to EBNA-1*, 30 Autoimmunity 53 (1999), filed as exhibit Y.
- Andrea 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 (1997), filed as exhibit 39.
- Cem Gabay et al., *Impact of Synthetic and Biologic Disease-Modifying Antirheumatic Drugs on Antibody Responses to the AS03-Adjuvanted Pandemic Influenza Vaccine*, 63 Arthritis & Rheumatology 1486 (2011), filed as exhibit QQ, tab 7.
- Neal A. Halsey et al., *Algorithm to assess causality after individual adverse events following immunizations*, 30 Vaccine 5791 (2012), filed as exhibit QQ, tab 9.
- Jens Hennecke & Don C. Wiley, *Structure of a Complex of the Human α/β 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. Experimental Med. 571 (2002), filed as exhibit 35.

- Eddie A. James et al., *Citrulline-Specific Th1 Cells Are Increased in Rheumatoid Arthritis and Their Frequency Is Influenced by Disease Duration and Therapy*, 66 *Arthritis & Rheumatology* 1712 (2014), filed as exhibit SS, tab 4.
- X. Li et al., *Influenza virus haemagglutinin-derived peptides inhibit T-cell activation induced by HLA-DR4/1 specific peptides in rheumatoid arthritis*, 24 *Clinical & Experimental Rheumatology* 148 (2006), filed as exhibit 37.
- Karen Lundberg et al., *Periodontitis in RA—the citrullinated enolase connection*, 6 *Nature Reviews: Rheumatology* 727 (2010), filed as exhibit 38.
- Vivian Malmström et al., *The immunopathogenesis of seropositive rheumatoid arthritis: from triggering to targeting*, 17 *Nature Reviews: Immunology* 1 (2016), filed as exhibit PP, tab 3.
- Paula Ray et al., *Risk of rheumatoid arthritis following vaccination with tetanus, influenza and hepatitis B vaccines among persons 15-59 years of age*, 29 *Vaccine* 6592 (2011), filed as exhibit CC.
- Carla G. S. Saad et al., *Immunogenicity and safety of the 2009 non-adjuvanted influenza A/H1N1 vaccine in a large cohort of autoimmune rheumatic diseases*, 70 *Annals of the Rheumatic Diseases* 1068 (2011), filed as exhibit QQ, tab 18.
- Daniel A. Salmon et al., *Association between Guillain-Barré syndrome and influenza A (H1N1) 2009 monovalent inactivated vaccines in the USA: a meta-analysis*, 381 *Lancet* 1461 (2013), filed as exhibit QQ, tab 19.
- Ami Schattner, *Consequence or coincidence? The occurrence, pathogenesis and significance of autoimmune manifestations after viral vaccines*, 23 *Vaccine* 3876 (2005), filed as exhibit EE.
- Omri 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 *Arthritis & Rheumatism* 2873 (2011), filed as exhibit SS, tab 3.
- K. Stratton et al., *IOM Committee Review Adverse Effects of Vaccines: Evidence and Causality*, National Academy of Sciences (2011), filed as exhibit SS, tab 2.
- Jian Sun et al., *Superior Molecularly Altered Influenza Virus Hemagglutinin Peptide 308-317 Inhibits Collagen-Induced Arthritis by Inducing CD4+ Treg Cell Expansion*, 64 *Arthritis & Rheumatism* 2158 (2012), filed as exhibit 31.
- Pia Svendsen et al., *Tracking of Proinflammatory Collagen-Specific T Cells in Early and Late Collagen-Induced Arthritis in Humanized Mice*, 173 *J. Immunology* 7037 (2004), filed as exhibit SS, tab 5.
- Barbara Szomolay et al., *Identification of human viral protein-derived ligands recognized by individual MHC-I-restricted T-cell receptors*, 94 *Immunology & Cell Biology* 573 (2016), filed as exhibit 73.
- Brett Trost et al., *No human protein is exempt from bacterial motifs, not even one*, 1 *Self/Nonsel* 328 (2010), filed as exhibit TT, tab 6.

L.A. Trouw et al., *Autoimmunity in rheumatoid arthritis: different antigens—common principles*, 72 *Annals of the Rheumatic Diseases* ii132 (2013), filed as exhibit 48.

Johanna Westra et al., *Vaccination of patients with autoimmune inflammatory rheumatic diseases*, 11 *Nature Reviews: Rheumatology* 135 (2015), filed as exhibit II.

Linda Wooldridge et al., *A Single Autoimmune T Cell Receptor Recognizes More Than a Million Different Peptides*, 287 *J. Biological Chemistry* 1168 (2012), filed as exhibit 69.