

# **Respondent's Exhibit R**



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April 24, 2007

## REPORT OF ROBERT S. FUJINAMI, PhD

As a description of my background and qualifications, I have a BA from the University of Utah in Microbiology with honors (1972), and received my PhD in Immunology from the Department of Microbiology and Immunology at Northwestern University (1977). My PhD thesis investigated mechanisms of how and by what means young (neonatal) animals can develop an inflammatory autoimmune disease of the central nervous system (CNS), known as experimental autoimmune (allergic) encephalomyelitis (EAE) (1-5). This is an experimental animal model for the human CNS demyelinating disease multiple sclerosis (MS) (6). I received additional post-doctoral training at Scripps Clinic and Research Foundation (1977-1981), now known as The Scripps Research Institute where Dr. Michael B. A. Oldstone was my fellowship mentor. During this time I investigated immune responses to measles virus and the mechanisms that could lead to measles virus persistence. Following my fellowship I took a position as Assistant Member (Assistant Professor) at The Scripps Research Institute (1981-1985). It was during my time at Scripps that I authored articles on measles virus persistence with Dr. Oldstone and developed the concept of molecular mimicry, an immune mechanism for microbe-induced autoimmune disease (7-13). In 1985 I moved to the University of California at San Diego as Associate Professor in the Department of Pathology and continued my research on molecular mimicry, virus induction of autoimmune disease, experimental autoimmune disease models for CNS inflammation and measles virus pathogenesis. In 1990 I moved to the University of Utah School of Medicine as Professor in the Department of Neurology and was also appointed adjunct Professor in the Department of Pathology. I conduct National Institutes of Health (NIH) and National Multiple Sclerosis Society (NMSS) funded research that focuses on virus-induced autoimmune disease, molecular mimicry, EAE, virus persistence that leads to immune-mediated disease, and for the past five years have investigated immune responses to CNS proteins and viruses in individuals with autism. I teach both medical and graduate students and give lectures on autoimmunity and viral pathogenesis, particularly measles virus pathogenesis.

I am presently and have previously been on and/or chaired various research grant review panels for the NIH, NMSS, National Science Foundation (NSF), and Canadian and European panels as well. I received a merit award (Jacob Javits Neuroscience Scholar Award) from the National Institute of Neurologic Diseases and Stroke (NINDS) at the NIH. I have been asked to speak to the Nobel Medica Research Forum (Stockholm), Institute of Medicine (Washington DC), and World Health Organization (Geneva) on virus-induced autoimmune disease in relation to vaccination. I am routinely asked to speak at various universities and national and international meetings (see CV). I am currently the vice president for the International Society of NeuroVirology. I have either served in the past or am currently an editorial board member and/or reviewer for many journals, such as *Science*, *Nature* and *The New England Journal of Medicine*, in the area of virology, neuroscience and immunology. The above information and additional information as well as my publications are provided in my CV.

I have reviewed the medical records of Michelle Cedillo, the expert reports and the literature cited by the petitioners as well as the relevant literature in the field. In this report I would like to first provide some background information and then address specific issues incorporated into the reports of the petitioners' experts.

### *Immune System*

The immune system has evolved to protect individuals from microbial infections and it also protects us from tumors and cancers. The immune response to microbes can be divided into two parts. The first part is called the innate immune response. This is the first line of defense against infection. For example, when one is vaccinated against measles, vaccine containing a crippled measles virus is deposited just under the skin. At the site of injection, the crippled or attenuated virus may start to replicate. Infected cells produce various proteins that can initiate the innate immune response. Two of the components of the innate immune response are white blood cells (WBC) called macrophages and natural killer (NK) cells. These cells are recruited to the site by proteins such as interferons (IFN)- $\alpha/\beta$  (type I) and other proteins called chemokines produced by the infected cells and infiltrating cells. These IFNs have antiviral activity, but also can activate other cells of the innate immune system. The NK cells produce and release a protein called IFN- $\gamma$ . This is a potent activator of macrophages which can engulf cells infected with measles virus and digest the viral proteins into small peptides. Other cells called dendritic cells also have engulfing and digesting properties. These dendritic cells are drawn to sites of inflammation, and in this example, engulf infected cells and viruses, and can take these to the draining lymph nodes.

The draining lymph node is where the adaptive or second line of defense is initiated. Here, other WBC called lymphocytes encounter the measles virus or viral proteins. Lymphocytes can be divided into several different populations. One population is the T cell. They are called T cells since they differentiate in the thymus. Another population is the B cell. B cells differentiate in the bone marrow. In our example, B cells when properly stimulated differentiate into plasma cells that produce proteins known as antibodies. Antibodies can bind to measles virus and "neutralize" it, rendering the virus noninfectious. Antibodies can also bind to measles virus and/or infected cells, and activate a cascade of different serum proteins known as complement proteins. Complement proteins can form holes or pores in the virus and measles virus infected cells, rendering the viruses noninfectious and killing the measles virus infected cells. T cells can be divided into two different populations dependent upon which surface protein markers are present. CD8<sup>+</sup> T cells have the surface marker CD8 and the ability to directly kill measles virus infected cells. Therefore, these cells are important effector cells in clearing the body of virus infected cells. CD4<sup>+</sup> T cells have the surface marker CD4 and are known as "helper" T cells. These T helper cells (Th cells) can be further divided into different populations by what proteins they secrete. Th1 cells tend to produce pro-inflammatory proteins, known as cytokines such as IFN- $\gamma$ . IFN- $\gamma$  can activate macrophages enhancing their ability to engulf measles virus and virus infected cells. Th2 cells tend to produce anti-inflammatory cytokines such as interleukin (IL)-4. Some Th2 cells have the ability to aid B cells to differentiate into plasma cells that produce measles virus reactive antibodies. Th1 and Th2 cells cannot be distinguished from each other by the surface proteins they express. To quantitate Th1 and Th2 cells the pro-inflammatory or anti-inflammatory proteins, cytokines, need to be measured in each cell using specialized techniques. These T cells can be modulated by T regulatory cells that can fine tune the immune response in a positive or negative way.

All T cells have proteins on their surface called T cell receptors that give each individual T cell the ability to recognize different peptides. T cells that recognize measles virus infected cells

recognize measles virus peptides by T cell receptors on the surface. Therefore, in our example, the measles vaccine is able to induce the production of anti-measles antibodies, T cells that produce various pro- and anti-inflammatory cytokines and T cells that can kill virus infected cells, such that the body is immune to subsequent measles virus infections.

### ***Autoimmunity and Autoimmune Disease***

Sometimes the body's immune system is fooled into attacking its own tissues. This is known as autoimmunity. If pathology or disease arises due to the "anti-self" immune response, this is called autoimmune disease. Examples of autoimmune diseases are type I diabetes, systemic lupus erythematosus, rheumatoid arthritis and multiple sclerosis. In type I diabetes, the immune response is directed against islet cells in the pancreas. When a critical number of islet cells are destroyed, diabetes will ensue. Autoimmune disease involves components of the innate immune system, such as the macrophage, and cells of the adaptive immune system such as T cells and B cells. A major part of my research is investigating the role viruses have in triggering autoimmune disease and what are the immune cells that mediate autoimmune disease.

### ***Measles Virus***

Measles is a disease caused by the "wild-type" measles virus, not the vaccine strain of measles virus. It is one of the most contagious viral infections known to man. The virus is usually acquired by inhaling small droplets containing the virus from other infected individuals due to coughs or sneezes. Once the virus enters the lungs it replicates locally and then disseminates to lymph nodes draining the lungs. Here, the virus replicates, and the virus is able to enter the blood system where either free virus or infected mononuclear cells spread the virus to other organs. The virus then can replicate in some of these other tissues, such as the skin. It is thought that the virus then again enters the blood stream and travels back to the lungs where it can then be transmitted to another individual through coughing or sneezing. The rash is caused by a certain population of lymphocytes (T cells) attacking virus infected cells in the skin. Infection with the wild-type virus can cause immunosuppression. My laboratory is investigating how measles virus induces this immunosuppression (14-17).

In very rare instances measles virus can establish a persistent infection. This is known as subacute sclerosing panencephalitis (SSPE). About one to two individuals per million infected with measles virus develop SSPE. Generally individuals are infected under the age of two with the wild-type measles virus, and the disease on average arises seven to ten years after infection. Measles virus has been identified in lymphocytes and brains of infected individuals [reviewed in (18)]. Most individuals with SSPE die from encephalitis. Universally, all individuals with SSPE have very high levels of measles virus reactive antibodies in the serum and in the cerebrospinal fluid (CSF). With the advent and use of the measles vaccine, SSPE has been virtually eliminated in the United States. There is no evidence that the measles vaccine can induce SSPE (18). Therefore, vaccination with the measles vaccine protects against persistent measles virus infection.

### ***Institute of Medicine Report***

In 2004 the Institute of Medicine of the National Academies published a report entitled "Immunization Safety Review: Vaccines and Autism." The Institute of Medicine was established by the National Academy of Sciences in 1970 to be an advisor to the federal government on issues of public health. The Immunization Safety Review Committee was established to review data about measles, mumps, rubella (MMR) vaccine and autism, and thimerosal and autism. Members of this

panel were selected by strict criteria. No members had a vested interest in vaccine safety questions and no members had participated in the development of a vaccine or evaluated a vaccine under study. The committee examined the hypothesis that vaccines, specifically MMR vaccine and thimerosal containing vaccines, are causally associated with autism. From the Executive Summary, “The committee concludes that the body of epidemiological evidence favors rejection of a causal relationship between the MMR vaccine and autism. The committee also concludes that the body of epidemiological evidence favors rejection of a causal relationship between thimerosal containing vaccines and autism. The committee further finds that potential biological mechanisms for vaccine-induced autism that have been generated to date are theoretical only.”

The committee also reviewed studies following immune deviation such as Th1 versus Th2 shift, in people with autism and reported, “In summary, although several studies have reported abnormalities of components of the immune systems, they have often had contradictory results, making it difficult to achieve a consensus on any specific immune abnormality that might characterize autism. More fundamentally, it is not clear how these abnormalities might explain the CNS defects in autism or whether they could be secondary to gastrointestinal or other complications of developmental disability.” Due to the conflicting reports, one cannot conclude that there is a consistent Th1 versus Th2 shift in individuals with autism.

### *Specific Experts’ Reports – Petitioners*

#### *Krigsman’s Report*

There are several points I would like to make concerning Dr. Krigsman’s report. Dr. Krigsman pointed out that the gastrointestinal (GI) and arthritic components of the disease noticeably improved following an immunosuppressive therapy of 6-mercaptopurine. However, in her report, Dr. Byers argues that Michelle Cedillo was already immunosuppressed. Dr. Byers stresses that the mercury in the vaccine previously received by Michelle Cedillo caused immune dysregulation that led to persistence of measles virus in the gut and that measles virus in itself was immunosuppressive. If this were the case, it is unclear why the GI and arthritic components of Michelle Cedillo’s disease were not resolved due to the persistence of the measles virus causing immunosuppression that should have alleviated these symptoms.

Dr. Krigsman also cites articles published by Dr. Andrew Wakefield about measles virus persistence in the GI tract of children with the regressive form of autism. Be that as it may, the Institute of Medicine (2004) in their report reviews the data put forth by Wakefield, and the Committee concluded that the “evidence favors rejection of a causal relationship between MMR vaccine and autism.” In the medical records supplied by Dr. Krigsman, there is a letter dated November 23, 2003, where Dr. Krigsman writes that “Michelle Cedillo is a patient of mine and under my professional care. She suffers from the dual diagnosis of autism and Crohn’s disease.” It is unclear why Dr. Krigsman only selectively cites the work by Wakefield purporting measles virus in the GI tract of individuals with autism and not the other work by Dr. Wakefield asserting that individuals with Crohn’s disease also have measles virus persisting in their GI tracts (19). Moreover, 10 of 13 authors on the original article by Dr. Wakefield describing the presence of measles virus in GI samples from autistic individuals have published an article describing their disagreement with the interpretation of the findings, and that the data did not support a causal link between MMR vaccine and autism (20). In addition the specificity of the assay used to detect the vaccine strain of measles virus is suspect (21).

Dr. Krigsman states that there is an established association between autistic spectrum disorders (ASD)-GI and vaccine strain measles virus. This is not a substantiated point. The Institute of Medicine has clearly evaluated the data about this, and it is not an established fact. In my opinion as well, there is not an association or causal relationship.

### ***Byers' Report***

The report by Dr. Byers describing the non-diagnosis of Crohn's disease contradicts that of the letter provided by Dr. Krigsman where he states that Michelle Cedillo has a dual diagnosis of autism and Crohn's disease. Thus, there appears to be some disagreement between Dr. Byers and Dr. Krigsman, as well as between Dr. Krigsman and himself.

It is my opinion that Dr. Byers is also over interpreting the immunological workup performed by Dr. Sudhir Gupta. The immunologic studies performed were compared to adult values. No comparison was made with age and gender matched control children values to determine whether there were "real" differences. These values could be better interpreted when compared to pediatric control values, and I would defer to Dr. McCusker for a more in-depth discussion of the pediatric immunology here. Another point is that Dr. Gupta states in the medical records that Michele has "almost normal immune functions." He does not specify that there is a skewing to a Th2 phenotype as Dr. Byers states. Dr. Gupta has published an article investigating Th1 and Th2 cytokines in individuals with autism (22). Dr. Gupta does not note any Th2 skewing in any of his summaries of Michelle Cedillo's immune status. Similarly, on October 24, 1997, Dr. Gupta told the parents that Michelle has a "perfect" immune system, which the mother noted in her diary. This would indicate that there is no Th2 skewing as opined in Dr. Byers' report. Enumeration of numbers of Th1 or Th2 cells (detecting cytokines in CD4<sup>+</sup> T cells) using specialized techniques has never been performed.

Dr. Byers' also states that "it is not surprising that several tests have shown it (measles virus) to be abnormally persistent in her body." This is not the case. The only evidence of measles virus persistence is a suspect assay (20) performed by Dr. O'Leary for measles virus RNA. In human cases of a persistent measles virus infection, SSPE, the antibodies to measles virus are extremely high. This is not found in any of the tests for antibody to measles virus described in the medical records of Michelle Cedillo. Dr. Byers' also opines that measles virus is immunosuppressive and reduces T cell reactions and causes broad activation of the immune system with spontaneous proliferation of lymphocytes. Such spontaneous proliferation of lymphocytes was not noted by Dr. Gupta in any of the immune tests that he performed. Such proliferation would skew his results and would have been obvious in the lymphocyte proliferation assays performed by Dr. Gupta. If Michelle Cedillo was immunosuppressed due to persistent measles virus, it is unclear why there was any need to treat her with immunosuppressive drugs. This logic is not consistent with the clinical picture provided by those who have evaluated Michelle Cedillo.

Dr. Byers also opines that thimerosal is an additional immunosuppressive factor, saying that the findings in Michelle Cedillo are consistent with the demonstration of an abnormal increase in the Th2 population of helper T cells resulting in a skewing of the Th1:Th2 ratio. Nowhere in the medical records, and particularly in Dr. Gupta's immunological analyses, were Th2 cells measured. Therefore, this statement is grossly incorrect. In other portions of the report, Dr. Byers states that there is an abnormal predominance of Th2 helper cells; again Th2 cells were never measured in Michelle Cedillo.

Dr. Byers is also confusing the effects of wild-type measles virus versus the vaccine strain. In the two articles on this matter in her report, Pan *et al* 2005 and Permar *et al* 2001, these

investigators are monitoring wild-type measles virus (Pan *et al* 2005, Bilhoven strain of measles virus in monkeys; Permar *et al* 2001, wild-type measles virus) and not vaccine strain where she is attributing the effects of wild-type measles virus to the vaccine strain, and is thus misrepresenting the data presented in the two articles. Dr. Byers in this section also misquotes data from the Sonoda *et al* 2002 report. She states that the study shows that measles virus genetic material was detected in the bone marrow aspirates from cancer patients. This part is correct. However, Sonoda *et al* 2002 conclude that there was no evidence of measles virus persistence and that the virus found in the bone marrow is consistent with wild-type measles virus currently in circulation. This is directly opposite to what Dr. Byers states in her report. Dr. Byers' conclusions are again misleading:

- a) Her first point is that there is a skewed Th1:Th2 ratio. Th1 and Th2 T cells were never measured in Michelle Cedillo.
- b) The second point is that immune dysregulation was acquired. She relies on the immunologic assays performed by Dr. Gupta to make this point. Dr. Gupta found that her immune system was "perfect." There is no evidence indicating a dysregulated immune system. Dr. Gupta's tests confirm this and the medical records point to normal immune responses to other vaccinations. For her to opine that the numbers of Th1 and Th2 cells are skewed, intracellular cytokine or ELISPOT assays would need to be performed. These assays were not conducted.
- c) The third point is that measles virus is found in the gut, and this is extrapolated to indicate that measles virus is in macrophages and lymphocytes and that these cells carry measles virus to the brain. There is no evidence that macrophages and lymphocytes harbor measles virus in Michelle Cedillo. There is no increase in measles virus reactive antibodies that would indicate a persistent infection.
- d) The fourth point is that persistent measles virus is responsible in part for her autoimmune gut disease. Dr. Byers has stated that measles virus causes immunosuppression. If Michelle Cedillo was immunosuppressed, she should not have been diagnosed with autoimmune diseases such as Crohn's disease, arthritis and uveitis. This appears not to be the case. There is no evidence in the medical records that there are pro-inflammatory cytokines in the brain of Michelle Cedillo. Further if there was such a skewing to a Th2 T cell response (anti-inflammatory), it is not clear how this would lead to a dysregulated immune system that secretes pro-inflammatory cytokines in the brain. Th2 T cells would be expected to secrete anti-inflammatory cytokines and promote B cell responses.
- e) The last point Dr. Byers states is that the measles virus vaccine strain is able to persist with pathologic consequences in the form of SSPE. This is clearly not the case. Since vaccination for measles was initiated, the incidence of SSPE (persistent wild-type measles virus) has dramatically been reduced, and those that do exist are due to wild-type virus.

The arguments used by Dr. Byers are not consistent within themselves and are at times mutually exclusive.

### ***Kinsbourne's Report***

I would like to address Dr. Kinsbourne's summation of Dr. Oldstone's review article published in *Virology* (2006) which starts with the section entitled Viral Persistence and Disease. While Dr. Kinsbourne provides quotations from the Introduction of the review, he seems to have

only provided selected portions of the text and not accurately captured the meaning of the passages. Dr. Kinsbourne then uses these as it applies to Michelle Cedillo's condition.

- a) His first point is that the immune response was weakened by the early exposure to mercury. There is no evidence that this is correct. Following the MMR vaccination, she made an appropriate immune response to measles, mumps and rubella proteins contained in the vaccine as evidenced by the titers measured in Dr. Gupta's lab. There is no indication that the immune response was suppressed.
- b) Dr. Kinsbourne states that the second foundation is the ability of the virus to infect differentiated or specialized host cells. Dr. Oldstone's second foundation is that viruses can acquire unique component(s) or strategies of replication. Be that as it may, there is no indication that Michelle Cedillo has persistent measles virus infection in her brain. There is the suspect finding by O'Leary that measles virus was detected in a gut biopsy. Persistent measles virus infection is associated with extremely high levels of antibodies to measles virus. There is no evidence of increased measles antibody titers in Michelle Cedillo; therefore, she does not have any evidence of a persisting measles virus infection.
- c) Dr. Kinsbourne's third point is that the disease that was caused, autistic regression, is novel and was previously unexpected. Again this is not supported by the data. Evidence demonstrates that the MMR vaccination did not and does not cause regressive autism, does not persist (no enhanced measles virus reactive antibodies) and is not present in lymphocytes or the brain.

In the next section – A single cause for ILNH and regressive autism, Dr. Kinsbourne cites work by Wakefield. Data provided by Wakefield about measles virus (vaccine strain) and autism is hypothetical as described in the 2004 Institute of Medicine review. Another petitioner's expert, Dr. Krigsman, has diagnosed Michelle Cedillo as autistic and having Crohn's disease. Although I defer to our gastroenterologist for a discussion of whether the diagnosis of Crohn's disease in Michelle Cedillo is correct, Krigsman's conclusion appears to be based in part on one of Wakefield's papers (19). As for Wakefield's assertion that the vaccine strain of measles virus persists in the GI tract of individuals with regressive autism (23), the reports associating Crohn's disease and measles virus are highly controversial and widely discounted.

Dr. Kinsbourne also cites Bradstreet *et al* (2004) where they claim that the vaccine strain of measles virus was found in brain or CSF. The Institute of Medicine has reviewed reports by Bradstreet and has found them not to be credible as to explaining a mechanism for MMR and autism.

Kinsbourne also opines that the virus is replicating in individuals with autism. If that were the case, high levels of measles virus reactive antibodies should be present in the serum as in persistent measles virus infection, SSPE, where wild-type virus is found in mononuclear cells and in the brains of infected individuals. This is not the case. There is no evidence that the vaccine strain of measles virus is present in Michelle Cedillo's brain or blood.

The medical records and tests do not support that mercury induced an immune dysfunction in Michelle Cedillo. Dr. Gupta has said that Michelle Cedillo has a "perfect" immune system. There is no evidence that the vaccine strain of measles virus is present in her CNS and caused or is causing autistic regression. In individuals with persistent measles virus infection, high levels of measles virus reactive antibodies are present in the circulation.

### ***Aposhian's Report***

In the report by Dr. Aposhian, he describes the various effects that mercury and its derivatives have on the body. He cites various studies where humans were inadvertently exposed to different forms of mercury. Individuals were followed for months to years after exposure. None of the reports found that individuals exposed to mercury were immunosuppressed and had a drastic increase in opportunistic infections or other infections such as colds. If mercury was such an immunosuppressive agent, a potent modulator of the immune response that allows the vaccine strain of measles virus to persist, an increase in other microbial infections would have been expected in the reports.

### ***Conclusion***

From the medical records, review of the literature and my experience in the field, it is my opinion to a medical certainty that the MMR vaccine and/or thimerosal did not contribute to Michelle Cedillo's medical condition of autism.

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Sincerely,



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