

## **Parainfluenza Virus-5: A New Paradigm and a Serious Host Challenge**

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Medical Committee

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As reported in the latest National CFIDS Foundation's press release, we have learned that Parainfluenza Virus-5 plays what the Foundation sees as a predominant and primary role in the development of CFS/CFIDS/ME. This is highlighted by both our own preliminary research, medical articles and dissertations, and most importantly by the highly advanced research completed by Dr. Steven Robbins.

In this article, we will try to convey several critical factors to our readers. Some data will refer to what is known about Parainfluenza Virus-5 (PIV-5). Other data will marry research completed in the field of CFIDS with that for PIV-5. Additional notes will be provided to fill in the blanks as necessary. In addition, we have chosen to not include supportive evidence for either Multiple Sclerosis or Epilepsy in this report.

Parainfluenza Virus-5 is the new name adopted by virologists for a virus that was previously known as Simian Virus-5 or SV5. The parainfluenza virus PIV-5 is a member of the paramyxovirus family of negative-strand RNA viruses that has an RNA genome of approximately 15,000 nucleotides.

SV5 was first isolated in 1956 from uninoculated rhesus and cynomolgus monkey kidney cell cultures. Very little attention was paid to this virus until the discovery of the hemadsorption method in 1957 which greatly facilitated the recognition of myxovirus infection in cell cultures. In 1959, the SA strain was obtained from the nasal washings of a human volunteer with a common cold showing acute upper respiratory infection. In 1959, the DA strain was isolated from a specimen obtained from a fatal case of infectious hepatitis. In 1963, a second DA strain isolate was made from monkey kidney cell cultures inoculated with the throat swab of a child suffering from respiratory illness. In 1970, an SV5 related virus was isolated from the brain cell cultures which were derived from biopsy specimens of a patient suffering from Creutzfeldt-Jacob disease.

Let us digress somewhat. As our conversations with Dr. Robert Possee at Oxford University matured in Spring 2003, one important factor came to the surface above everything else. Of course by that time Dr. Yoshitsugi Hokama's work was underway. We knew from his preliminary results that the ciguatera epitope played an important role in the disease process but the exact nature of this needed to be elucidated. Our funding for Dr. Hokama came on the heels from our discoveries made through careful examination of Dr. W. John Martin's world patent which divulged his use of the ciguatera monoclonal antibody to detect his "stealth virus" in CFIDS patient blood. By bringing this work to scientists at Oxford, we found our conversations

centered around epidemiology more and more! As of late April 2003, we chose to examine two paths for obtaining further information that we felt would be most helpful and would add clarification to this problem; CFIDS epidemiology and the current research of Dr. DeMeirleir's. The first was to examine the work of Dr. DeMeirleir who previously had confirmed the aberrations in RNaseL, a key component in the antiviral pathway, which had been based on prior work completed by Dr. Robert Suhadolnik at Temple University. The NCF also carefully examined Dr. DeMeirleir's book and learned of the Stat-1 protein defect. Most importantly however, we found the patent associated with his finding which provided additional explanations and information that had been left out of the book!

Within days of reading the patent, the NCF contacted three major scientists who had completed extensive research work in the Stat-1 field. The first two had been mentioned in a previous column written for Forum readers. They were Dr. Joan Durbin from Columbus Children's Research Institute and Dr. David Levy from New York University School of Medicine. Both scientists had been responsible for the development of one of the first animal models for Stat-1 deficiencies and both were well published in the field. The other scientist we discussed this with was Dr. Curt Horvath, from Northwestern University, who also had published extensively in the Stat-1 field. The NCF shared Dr. DeMeirleir's data with each of these scientists. Each had commented on how unfortunate it really was that Dr. DeMeirleir hadn't published his findings in a peer-review journal. What the NCF had learned some time ago applied once more. Peer-review was a touchy subject for those who desired to protect their intellectual property rights. Given that Dr. DeMeirleir first found the lack of Stat-1 protein in CFIDS patient blood, that it appeared to correlate with RNaseL, and that it underwent proteasomal degradation, we asked each of the three researchers if they thought that a virus could be directly involved in this activity. Fortunately, we received some excellent feedback.

During this time, the NCF created a "short list" that included viruses that were known to directly attack and degrade the Stat-1 protein as part of their viral evasion strategy. Stat-1 degradation has been seen as a means for providing interferon antagonism by certain viruses as a method to escape the host's immune response. As a direct consequence of this process, one specific virus rapidly rose to the top of our list and that was Parainfluenza Virus-5 (PIV-5), also previously referred to as Simian Virus-5 (SV5) in the published medical literature.

By this time the NCF had provided Stat-1 evidence, from various medical journal articles, to both Dr. Konnie Knox and to Dr. Donald Carrigan to see if they had an interest in pursuing this type of research. They subsequently filed a research application with us that received formal approval and research funding via our Research Grant Program. Both scientists were off and running as they would soon be exploring the possible role of Stat-1 in CFIDS.

During this same time period, the NCF had also contacted Dr. Robert Suhadolnik directly regarding Dr. DeMeirleir's Stat-1 finding. In fact, Dr. Suhadolnik informed the NCF that he was in communication with Dr. DeMeirleir regarding Stat-1 and he inquired as to whether the Stat-1 findings were to be published in peer-review. Dr. Suhadolnik would later inform the NCF that his group subsequently tested for the Stat-1 protein in CFIDS patient

samples that had been provided to them by NIH physicians and researchers. These samples were found to be deficient in Stat-1 echoing the importance of Stat-1 in CFIDS. Dr. Suhadolnik had also commented that Stat-1 acted as a "front-end component" to RNaseL and the antiviral pathway. Though Dr. DeMeirleir's finding for Stat-1 was published in his book, a book in which Dr. Suhadolnik contributed a written chapter, Dr. Suhadolnik had commented to the NCF that he himself had been unaware of the Stat-1 information provided in the book!

Fortunately, with feedback from Drs. Durbin, Levy, and Horvath, the NCF went on to examine everything that was written in the PIV-5 field. Our primary informational sources included the National Library of Medicine, both the U.S. and World Patent databases, the CRISP database, the U.S. and World Dissertation databases, as well as biological tools such as Genbank and BLAST. Of course important books, such as Field's Virology, also made their way onto our bookshelf. The NCF had read every possible piece of information that they could get their hands on. We felt that ultimately the knowledge gained from this information along with the scientific verification or proof that would accompany it would become the driving force for changing the very nature of this disease. In other words, the NCF felt that the combination of information and scientific proof would become the primary means to an end for providing legitimate answers to a disease that had boggled researchers for decades and had destroyed the lives of patients worldwide.

Late in the summer of 2003, we first learned of Dr. Steven Robbins' research in Australia. Dr. Robbins was a virologist with the Neurovirology Research Unit of the Sir Albert Sakzewski Virus Research Centre associated with the Royal Children's Hospital in Herston, Queensland in Australia. The NCF had learned that Dr. Robbins had obtained his Ph.D. from the University of Kansas in 1978. His dissertation was titled "Proteins Associated with Measles Virus Nucleocapsids in Acute and Chronic Infections." We found this interesting because measles and PIV-5 are both viruses from the paramyxovirus family.

In Australia, Dr. Robbins had used viral isolation techniques to assist in the identification of this new virus. The entire virus was then sequenced using PCR techniques and was subsequently identified using Genbank. His research highlighted Multiple Sclerosis, Epilepsy, and CFIDS. This knowledge came directly from his world patent and from Security and Exchange Commission documents filed by the companies involved in this research as well as from press release documents that were available from corporate websites. Of significance to the NCF was the fact that Dr. Robbins, backed by legal U.S. corporations, had approached the FDA for approval for a test that had been developed to identify this pathogen in humans. This test would have wide ranging consequences for patients because of its direct association with these diseases. Attempts by the NCF to learn of the current status of this test at the FDA have failed.

With the Stat-1 work underway by Drs. Knox and Carrigan, the NCF began to share information on PIV-5 with them. As it would turn out, Dr. Carrigan had received his Ph.D. from the University of California at San Francisco in 1979. His dissertation was titled "Experimental Chronic Myelitis in Hamsters Associated with a Variant of Measles." The NCF

felt that this was a real plus because Dr. Carrigan also had experience with paramyxoviruses. As a consequence, both Dr. Carrigan and Dr. Knox were interested in pursuing this additional research. Ultimately, they provided the NCF with a research proposal titled "Potential Role of Persistent Paramyxovirus Infection in CFS." The NCF had also provided them with additional funding as the result of an addendum that was added on to their original proposal. Their scientific research would therefore come to encompass both Stat-1 and PIV-5. Furthermore, the NCF would also gain valuable insight into possible interactions between HHV-6 and Stat-1. Interestingly, double infections have been demonstrated with PIV-5 and herpes viruses.

As time progressed, the NCF began to closely examine the nucleotide sequence data from Dr. Robbins' research. From what we have been told, an independent company had sequenced the entire virus that Dr. Robbins had isolated. One key protein, known as the fusion protein, was associated with viral infection of host cells. Though Dr. Robbins had identified this viral component of Cryptovirus as a porcine rubulavirus, the NCF wanted to know the originating source. In other words, what was the source of the infection? Where did it come from? By running this sequence through BLAST, a tool used to identify nucleotide sequence matches in Genbank, an NIH database, the NCF had learned that the fusion protein from the viral isolate that Dr. Robbins had identified (Genbank Assession number AX586949) had in-fact matched 100% with that for the fusion protein for the SER strain of PIV-5 (Genbank Assession number AJ278916). The SER strain had first been discovered in 1994 by three scientists at Bayer AG in Germany who had isolated it from swine with PRRS or Porcine Reproductive and Respiratory Syndrome. Additional nucleotide sequencing for the SER strain of PIV-5 had been completed by Dr. Hans-Dieter Klenk at the Institute for Virology at Phillipps University in Marburg, Germany and Dr. Christoph Klenk at the Institute of Pharmacology at the University of Wurzburg in Wurzburg, Germany. It is important to note that the SER strain had initially been characterized as PIV-2 but was subsequently classified as PIV-5.

Simply stated, it now appeared that Dr. Robbins' virus that he had isolated from very ill patients potentially came from swine! This discovery would make this virus an animal or zoonotic virus, a virus that had crossed-over from one species (animal) to infect another (people)! Interestingly, this would be no different than the current focus on the bird flu in the media and the concerns about it infecting people! Likewise, current media attention given to the mumps virus, a rubulavirus similar to PIV-5, and its rapid spread in the Midwest was also found to be equally worthy of growing public awareness. The NCF pondered, "Should Cryptovirus/ PIV-5 receive any less airplay?"

The NCF wondered if this was a plausible explanation? After careful consideration our conclusion was "Absolutely!" It made sense to us here at the NCF, along with the many scientists who we shared this information with, largely because of the following logic: If you can have the swine flu (swine influenza) then you certainly can have swine parainfluenza! These types of infections have been involved in epidemics and pandemics throughout history. Hmmm, CFS was also previously called the "Yuppie Flu!" Pretty close if you ask us!

After running these sequences through BLAST, the NCF began to ask additional questions. Why would running Dr. Robbins' viral fusion sequence through BLAST generate a 100% match with that for the fusion sequence for the SER strain BUT when you ran the fusion sequence for the SER strain through BLAST, Dr. Robbins' fusion sequence is NOT returned and listed as a possible match even though it actually is a 100% match? The NCF has shown this to several research people who use this tool daily and they have run these BLAST sequences on their own and have questioned this much like us! After all, BLAST acts as a sophisticated pattern recognition program that shouldn't depend on the source of the data. So, we naturally began to wonder if this could actually somehow represent scientific misconduct or a cover-up of some type at the national/federal level or is it just some type of error in the BLAST program or perhaps an unfriendly user error? At this point we just don't know? Certainly it doesn't make any sense because any scientist who would run this sequence through BLAST looking for sequence matches would never learn of Dr. Robbins' own sequence discovery. Therefore, should our interpretation of this situation be correct, scientists may perhaps never associate this swine virus with human disease. We also wondered if this was an isolated sequence that this happened to? As it would turn out, it wasn't. The fusion protein filed in Genbank from the original scientists at Bayer, as part of their patent, also didn't return a sequence match for that from Dr. Robbins' research. This is something that the NCF continues to ponder over.

Next, the NCF's funded research progressed to where Dr. Konnie Knox made a formal presentation at the Seventh International AACFS Conference on Chronic Fatigue Syndrome, Fibromyalgia, and other Related Illnesses in October 2004. There, Dr. Knox presented data on the "Deficiency in the Expression of Stat-1 Protein in a Subpopulation of Patients with CFS."

With the new year, 2005 would ultimately bring exciting information to the NCF. Dr. Knox and Dr. Carrigan had performed numerous tests for the Foundation which included antibody as well as PCR specific probes. As stated in our press release, antibody testing provided some initial hints however a PCR specific probe picked up the infection in a former patient of Dr. David Bell's and Dr. Paul Cheney's. The NCF realized that this longtime CFIDS patient had their spleen removed years ago due to hemolytic anemia. This perhaps aided in PCR detection due to the fact that cells that circulated in the marrow could reach the periphery due to the lack of a spleen. Amazingly, many years prior this very same patient had been labeled by Dr. Thomas Evans, then Head of Infectious Diseases at the University of Rochester's School of Medicine, as an HIV-negative AIDS patient. This patient had profound immunosuppression and it was Dr. Cheney who had identified this patient as one with ICL or idiopathic CD4 lymphocytopenia. Recent bone marrow biopsies from this patient have served to confirm several problems in the bone marrow compartment. PIV-5 has been known to infect bone marrow cells according to the medical literature.

Though Drs. Knox and Carrigan had used PCR for identification of the fusion protein for PIV-5 in this patient, the NCF climbed the virology ladder to share this data with Dr. Robert Lamb. Dr. Lamb is a Professor of Molecular and Cellular Biology at Northwestern University. He is also Professor of Microbiology-Immunology at Northwestern University's Feinberg School

of Medicine as well as an Investigator at the Howard Hughes Medical Institute. Dr. Lamb is a past president of the American Society for Virology and is co-editor of Field's Virology. In our communications with Dr. Lamb, he informed us that there were only three scientists who had isolated PIV-5 in human blood. These included Dr. Edith Hsiung at Yale University, Dr. Richard Randall at the University of St. Andrews in Scotland, and Dr. Steven Robbins. The NCF learned from Dr. Lamb that we had unequivocally found the virus in this patient. We were very grateful for this feedback. The NCF was then able to track down one of Dr. Hsiung's colleagues at Yale University. Dr. Marie Landry, who is Professor of Laboratory Medicine and Director of the Virology Laboratory at Yale, encouraged the NCF to stay focused and to remain on the trail of PIV-5. Dr. Landry told us that Dr. Hsiung felt very strongly that PIV-5 played an important role in human disease. As the NCF's confidence began to grow though, we realized certainly that we had much more research to do. We concluded however that Dr. Knox and Dr. Carrigan had helped us to reach a new intermediate point in our research by providing what the NCF felt was some preliminary evidence that supported Dr. Robbins' discoveries. The NCF had also concluded that spinal fluid and bone marrow biopsy samples would greatly assist in the detection of this virus.

Along this part of the journey, the NCF had learned several things. One is that very few reagents were available to researchers for PIV-5. This was a field where special monoclonals and other reagents had evolved over time and therefore had been developed by those scientists who had worked in this field for many years. Typically, these reagents weren't shared with researchers outside the field. Next, we learned that fewer than 300 journal articles existed for PIV-5 in the National Library of Medicine. That represented "slim pickings" at best. Lastly, the NCF was appreciative of what Drs. Knox and Carrigan were trying to do and that was to develop their own specific technologies to directly support our research grant. RNA viruses such as this one mutate and trying to hit a moving target by developing a research test isn't exactly an easy task. It's a high-wire balancing act between specificity and sensitivity, just two hurdles from the many technical considerations that had to be made.

From our information sources, the NCF had also learned that some strains of PIV-5 appeared to cause an acute but limited illness while other strains caused viral encephalitis and neurological disease. The NCF had discovered that some of the encephalitic strains of PIV-5 could directly infect ependymal cells. Ependymal cells are the cells that line the ventricles of the brain as well as the central canal of the spinal cord. Dr. Robbins had determined that the virus directly infected B-cells and that these cells acted as a reservoir for the virus. The scientists at Bayer concluded that this virus was involved in respiratory and reproductive diseases. This was due to the fact that this virus was classified as a parainfluenza virus. Parainfluenza viruses are known to adversely affect the respiratory system. Furthermore however, this virus was in the genus rubulavirus. Rubulaviruses, such as mumps, are known to adversely affect the reproductive system. Several years ago, the NCF had the good fortune of having numerous conversations with Dr. John McClaskey, an endocrinologist and pathologist with Rochester General Hospital, who had completed his residency at the NIH. Dr. McClaskey told the NCF that virtually every male, with long-standing CFS that he had examined at the NIH, suffered from hypogonadism and that these men were unable to generate testosterone. This is consistent

with orchitis and hypogonadism associated with another rubulavirus, mumps. This is proof perhaps that the research world does meet up eventually with clinical practice! Of additional interest, it is important to note that rubulaviruses have also been associated with Chiari malformation, hydrocephalus, viral myocarditis, and nephritis.

How then could a single virus be involved in diseases such as CFIDS, MS, and epilepsy? First of all, these viruses differ by strain variations. For example, HHV-6 has both an A-variant as well as a B-variant. Each has their own unique characteristics even though they are part of the same virus family. With mumps, a dozen strains have been identified. This is really no different than PIV-5 where some strains have been associated with encephalitis while others have caused limited illness. Secondly, we suspect that even variations within a disease could also occur simply because RNA viruses mutate. With each replication cycle, this virus is capable of mutating to subtly change some of its characteristics. These changes will likely translate into changes that can then occur in the host. In other words, this virus acts just like a "cunning chameleon." Lastly, it may turn out that animal strains of the virus, that are capable of infecting people, may have a greater propensity to mutate since they probably did so to jump species initially. As you can now appreciate, virology involves very tedious work!

Let us turn our attention to PIV-5 and discuss some of its unique characteristics. The SER strain of PIV-5 is unusual because it exhibits no observable cell fusion activity in several cell types. Simply stated, this SER strain fails to induce syncytium formation. Syncytium formation means that the uninfected cell and the infected cell fuse together to form a multinucleated giant cell. The SER strain lacks this characteristic! Scientists have determined that this apparent lack of fusion activity is the result of an alteration to the SER fusion protein.

Next, PIV-5 directly targets two important components associated with the innate immune response. The first target has already been discussed and that is the Stat-1 protein. Since Stat-1 is responsible for type I and type II interferon responses (alpha, beta, and gamma) within the cell, its role in cellular immunity cannot be understated. Medical science has revealed that Stat-1 deficient cells are unresponsive to interferons thus leaving the host defenseless against viral and bacterial infections. PIV-5 directly targets and degrades Stat-1 via one of its viral proteins known as the V protein. This V protein of PIV-5 acts to block interferon signaling. This is an important part of its viral evasion strategy against the host. Because of this strategy, the Stat-1 deficiency seen in patients with CFIDS represents an acquired host condition due to viral infection by PIV-5. Dr. DeMeirleir had previously identified a correlation between Stat-1 and RNaseL ratios. RNaseL is an important component of the antiviral pathway. It is worth noting that Ampligen is a mismatched double-stranded RNA (dsRNA) based interferon inducer. The V protein of PIV-5 has been shown to block intracellular dsRNA signaling thus limiting the yield of beta-interferon during infection.

The second target associated with PIV-5 is IRF-3. IRF-3 is notation for interferon regulatory factor-3. The mechanism associated with IRF-3 can best be described as follows. When a virus infects a cell, double-stranded RNA (dsRNA) activates the transcription factor IRF-3 which then stimulates type I interferon (alpha/beta) gene expression. The V protein

of PIV-5 acts to block interferon production by blocking IRF-3. The blocking of IRF-3 is a strategy employed by another virus, hepatitis C (HCV).

To summarize, PIV-5 blocks two distinct pathways of the innate immune response due to the fact that its V protein blocks both interferon signaling, by causing the degradation of Stat-1, and interferon production, by blocking IRF-3 nuclear import. Therefore, PIV-5 infection acts as an interferon antagonist in the host. It is important to remember that for persistent infections to become possible, viral inhibition of host defenses must play a significant role in the viral evasion process. We believe that these are the characteristics that potentially make PIV-5 a very formidable virus.

As we mentioned earlier in this article, after conversing with Oxford University scientists, epidemiologic considerations moved to the forefront. The NCF found an excellent and intriguing medical journal article titled "Risk Factors Associated with Chronic Fatigue Syndrome in a Cluster of Pediatric Cases." This was written by Dr. David Bell and colleagues who represented the Monroe County Health Department in upstate New York, the University of Rochester School of Medicine, as well as Roswell Park Memorial Institute. Here, the authors discussed pediatric CFS cases associated with the Lyndonville outbreak. In this paper the authors stated, "Highly significant positive associations were observed for the presence of other family members with symptoms of CFS, ingestion of raw milk either recently or in the past, ingestion of raw eggs, and history of allergies or asthma. Exposure to hot air heating, the presence of cats on the property, and appendicitis also had significant positive associations with CFS. The presence of dogs in the house was inversely associated with CFS." As a result of their study, these authors concluded that, "These data suggest that a combination of host and environmental factors, including an infectious agent or agents, are involved in the etiology of CFS."

Let's take a look at each one of these associations that were found to be highly significant and provide our interpretation based on what we have learned about paramyxoviruses. First, the presence of other family members with symptoms of CFS certainly suggests an infectious agent. Paramyxoviruses are known to be contagious diseases. Anyone who has witnessed the spread of measles or mumps in children in families can attest to this. These are perhaps the most commonly recognized paramyxoviruses. So having other family members with CFS symptoms is consistent with a paramyxovirus. Secondly, ingestion of raw milk either recently or in the past as well as ingestion of raw eggs suggests an infectious agent that is passed from a farm animal, such as a cow or a chicken, to humans. As we have pointed out and as the medical literature suggests, a zoonotic virus that passes from animals to humans would fit that for a paramyxovirus. Third, the history of allergies or asthma would be consistent with a paramyxovirus (parainfluenza virus) due to the respiratory nature of the infection. In fact, a recent medical article has provided new insight into this very process. In a medical model associated with asthma, chronic bronchitis, and chronic obstructive pulmonary disease, it was found that respiratory paramyxoviruses can cause a "hit and run" phenomenon that is manifested by the development of a permanent airway disease phenotype long after the infection has cleared. Can you imagine what happens when a paramyxovirus infection becomes persistent?

Fourth, exposure to hot air heating would be consistent with an airborne pathogen. One definition we found for paramyxoviruses was the following. Paramyxoviruses are a group of RNA viruses that are responsible predominantly for acute respiratory diseases and are usually transmitted in an airborne manner. Fifth, the presence of various associations with cats and dogs should not come as a surprise. Paramyxoviruses are known to infect numerous animal species so any association with common animals would not be surprising. Given the possible association with cows and chickens makes us wonder if any of these other animals in the Lyndonville study included feral cats, known to live in barns in rural communities. Lastly, what about appendicitis? Well, believe it or not, paramyxoviruses have been found to be associated with appendicitis. In the medical literature, there were several articles associating measles with appendicitis. In summary, the NCF is confident that paramyxoviruses provide an attractive epidemiologic fit for CFIDS, especially after examining the data from the cluster of pediatric cases associated with the Lyndonville outbreak.

A prominent feature of CFIDS is a dysregulated immune system. As such, one research article that the NCF took particular interest in involved that from Dr. Charles Lapp and colleagues. In this study, the researchers chose to examine apoptosis, also known as programmed cell death, in the lymphocytes of patients. Also measured was alpha-interferon as well as the interferon-induced protein kinase RNA (PKR). The authors concluded that increased apoptotic cell population was observed in patients compared to healthy controls. In fact, this increased apoptotic subpopulation in patients was accompanied by an abnormal cell arrest in the S phase and the G2/M boundary of the cell cycle as compared to the control group and these effects were mediated by PKR. The cell cycle or cell division cycle is the cycle of events in a eukaryotic cell from one cell division to the next. It consists of interphase, mitosis, and usually cell division. As cells proceed through this process, a surveillance system of checkpoints monitors the cell for damage and failure to perform critical processes. Checkpoints can block progression through the phases of the cell cycle if certain conditions are not met. What the NCF found most interesting is that this finding for cell cycle and apoptosis in-vivo in patient blood is in agreement with in-vitro research published by Dr. Robert Lamb. The infection of cells by viruses can affect the cell division cycle of the host cell to favor viral replication. In Dr. Lamb's article, PIV-5 was found to affect cell cycle progression in a manner identical to that described in CFIDS patients by Dr. Lapp.

Thus, Parainfluenza Virus-5 infection produces deleterious effects on the host due to the following characteristics. First, PIV-5 compromises immunity due to the virus's ability to directly infect B-cells which serve to act as a reservoir for the virus. Secondly, PIV-5 further compromises immunity due to interferon antagonism. Third, PIV-5 can induce serious immune suppression. Since the virus is capable of infecting bone marrow cells, the bone marrow compartment and its corresponding microenvironment is therefore compromised. The ability to subsequently generate appropriate cell lineages is adversely affected. Fourth, PIV-5 alters the cell cycle to affect apoptosis in infected cells. These various characteristics make for a powerful and distinctive combination of viral evasion strategies aimed at avoidance of and alteration to the host's immune system.

At the NCF, we had decided to take things a step further in our understanding of this virus so we turned to the medical literature for information about porcine rubulavirus. There we learned that swine suffered from interstitial pneumonia and encephalitis; that T-cells late in infection do not acquire CD8 phenotype (which probably accounts for the CD8 depletion); that in immunosuppressed convalescent swine, viral RNA was found in the brain and lung after recovery from acute infection and that the viral genome is active in these pigs; that there are alterations in the numbers of T-cells and B-cells in this infection; that boars experimentally infected with porcine rubulavirus formed lesions in their reproductive tract with testicular atrophy, degeneration of the seminiferous tubules, reduced sperm motility and quality, with overall results indicating that porcine rubulavirus caused severe epididymo-orchitis; that porcine rubulavirus can establish persistent infections in porcine kidney cells; that porcine rubulavirus is an emerging virus responsible for meningoencephalitis, respiratory distress, and reproductive alterations in pigs; that porcine rubulavirus causes the induction of apoptosis as an important mechanism in the pathogenesis of this infection and that this virus induces changes in lymphocyte subpopulations in peripheral blood. To us, this certainly was in agreement with our observations for our disease as CFIDS patients.

Is there any dedicated current research being done on the SER strain of Parainfluenza Virus-5? Yes, but it comes with many questions. According to the CRISP database, an NIH grant was given to Dr. Richard Compans. Dr. Compans is a Professor and Chair of Microbiology and Immunology at Emory University's School of Medicine. Dr. Compans' grant, funded by NIAID, began on July 1, 1997. His grant titled "Regulation of Viral Membrane Fusion" is funded through January 31, 2009. The NCF found this to be very interesting for several reasons. First, Dr. Compans received his grant in 1997. The scientists at Bayer AG in Germany hadn't had their research accepted for publication to the Archives of Virology until July of 1998. This was one year after Dr. Compans had received funding from NIAID. Therefore, the NCF asked, "Where did Dr. Compans get his informational heads-up from because this strain had never appeared before in any of the medical literature?" We speculate that perhaps this came from either the World or the U.S. patent applications that had been filed during 1994 and 1995 respectively. Perhaps information came from colleagues at either the NIH or the CDC? We just don't know. Secondly, the way the NCF looked at this, a twelve-year grant represented a pretty big chunk of change for a virus that hadn't been noticed by the scientific community yet! In other words, why would NIAID spend big money to research this virus? What did they know? Third, publications by Dr. Compans on this SER strain included colleagues at the CDC. So, the NCF came to realize that the NIH knew about this strain via the grant from NIAID. The CDC knew about this strain because of the publications from people who assisted Dr. Compans in his work. Granted, the NCF hasn't been able to find out the grant amount for this twelve-year project, but we're working on it! As a side-note, we also found it interesting that Dr. Compans was a co-editor along with Dr. Brian W.J. Mahy for a book titled "Immunobiology and Pathogenesis of Persistent Virus Infections" that was published in 1996. Dr. Mahy, as you may recall, was the former Director of the Division of Viral and Rickettsial Diseases at the CDC who was reassigned due to deceptive accounting practices. Implicated were the misappropriation of funds for CFS. Last of all, the NCF wondered about the potential impact regarding the findings for the SER strain of Parainfluenza Virus-5 in Porcine Reproductive and Respiratory Syndrome

(PRRS). PRRS outbreaks have occurred on several continents. According to an article published in 2005, "PRRS affected breeding herds and growing-pig populations as measured by a decrease in reproductive health, an increase in deaths, and reductions in the rate and efficiency of growth....PRRS imposes a substantial financial burden on U.S. swine producers and causes approximately \$ 560.32 million in losses each year." The NCF now realized that since this SER strain had first been identified in swine and apparently now in humans, this puzzle piece would carry with it serious ramifications, especially if we were dealing with a pandemic. For all those dealing with this disease, this would alter their lives forever often making it a true living hell.

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