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XMRV & AMPLIGEN

A Report from the 9th Hemispherx Biopharma Investigators Meeting

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- Gene Sequencing in Persons with CFS
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Gene Sequencing in Persons with CFS

Wendy Fallick, our research coordinator, and I have just returned from the 9th Investigators Meeting sponsored by Hemispherx Biopharma, makers of Ampligen and Alferon. This was perhaps the most exciting of these meetings that I have attended, and I suspect that information relayed this past week to us will change the field of medicine forever. I want to share that information with you.

Recall that Lombardi, Mikovits, et alia published a paper in the October 2009 Science journal describing a novel retrovirus in 67% of 101 patients with CFS, using a PCR (polymerase chain reaction) test. By checking for antibodies, viral protein, and direct viral culture they were able to demonstrate this virus in 95-98% of PWCs (persons with CFS).

This virus was called XMRV because of its special characteristics: Xenotropic because it first developed in another animal species but now infected only humans; Murine because it first developed in mice; and RetroVirus because it replicated backwards unlike most other viruses. In fact, XMRV was related to a family of murine leukemia viruses, or MLVs.

The Science paper was followed by several other reports that the virus was not found in other cohorts, and confidence in the Lombardi-Mikovits report was waning. Then Drs. Lo and Alter published a 2010 paper that identified by PCR a similar retrovirus in 86.5% of persons with CFS that they had studied. **The viruses that they identified were MLVs, only 2-3 base pairs (.00025 %) different from Lombardi's XMRV.**

This difference has been explained as a "shift" in the genome attributed to time and distance. That is, over time viruses tend to mutate slightly, and it is not exceptional for viruses from one geographical region (Lombardi/Mikovits on the West Coast) to differ slightly from those in another region (Lo/Alter, East Coast). This was seen, for example, in the 2009 swine flu epidemic where over 50 different strains of H1N1 were identified from Hong Kong, Singapore, Malaysia, etc.

There are two retroviruses thought to be pathogenic in man:

- HTLV Human T-Lymphotrophic Virus (4 strains but only 1 is harmful to man)
- HIV Human Immunodeficiency Virus (2 strains but only one causes AIDS)

And now we have to add MRVs or MLVs (Murine Retroviruses or Murine Leukemia Viruses) to the list. There are several strains of MLVs of which XMRV is one strain. Which strains are pathogenic in man has not yet been determined, although XMRV has been linked to familial prostate cancer at the least.

Let's turn for a second to a schematic representation of DNA and XMRV. DNA is made up of two twisted strands of nucleic acids strung together like beads. Only 4 nucleic acids are involved: Adenine, Cytosine, Guanine, and Thymine – or A,C.G and T – and their pattern along a single strand of DNA might look like :

ACGTACGTACGTACGTACGTACGTACGTACGTACGTACGTACGTACGTACG
T

XMRV is an RNA virus, or strand of nucleotide sequences very much like a single strand of DNA. Sections of each strand are named for their specific functions. A strand of XMRV may be represented as :

5' - LTR - US - gag - pol - env - U3 - LTR - 3'

Notice that there is a head ("five prime") and a tail ("three prime") and both ends are marked by a section called the "long terminal repeat" or LTR.

Most viruses replicate themselves starting from the 5'end to the 3' end. Retroviruses, however, use "reverse transcriptase (RT)" to replicate backwards (retro) inside a host cell to form a strand of DNA. This strand then incorporates itself into the host's own genomic DNA by an enzyme called "integrase."

Thus human DNA +XMRV ends up looking like:

ACGTACGTACGTACGT-LTR-US-gag-pol-env-U3-LTR-CGTACGTACGTACGTACGT

This new combination DNA is called a **"chimera"**. Now **human DNA contains millions of nucleotides, and XMRV only contains about 8000 nucleotides**, so the chimera is not as easy to spot as it appears here

Incorporated into your genome like this the virus may take control of the cell, manufacture abnormal proteins, and – in the case of XMRV – kill the cell. This latter event is called "apoptosis."

Lastly, unlike **the HIV retrovirus** that **multiplies rapidly** and **millions can be found in a single drop of blood**, **XMRV replicates slowly** and is **present in only very small amounts in the peripheral blood**.

These characteristics of XMRV can explain several observations:

- Very few XMRV particles are found in a blood sample and it may take multiple samples to find them
- Inside the cell and/or chimera, the XMRV is relatively protected from detection by the immune system and many blood tests
- When PWCs are very sick their white blood cell populations decrease (due to apoptosis)
- The XMRV particle is so small it can infiltrate virtually any part of the body and any system
- Why researchers are finding abnormal proteins in the blood and CSF of PWCs (proteomics)

Now, here is the most intriguing part of our Hemispherx meeting. It took hundreds of scientists at multiple sites ten years to map out the **3 billion nucleotides in the normal human genome**. Dr. Carter introduced us to Howard Urnovitz, CEO of **Chronix Biomedical**. **Urnovitz** revealed that his research group **is able to map genomes at a very rapid pace.** He expects that in the near future, Chronix will be able to map your entire genome in under six hours and for probably less than a $100 fee. This is StarTrek medicine!

Urnovitz went on to explain that **when apoptosis occurs, chimeras are spilled into the blood stream and can be extracted easily** by his laboratory. **When his lab examined the genomes of persons with CFS they found chimeras made up of XMRV genes (but oddly missing their LTR regions).**

This technology is wonderful news for PWCs because if XMRV or MLV can be clearly shown to cause CFS, then we will have an inexpensive and unique marker for the disorder!

The Chronix test is not currently available commercially, but Hemispherx plans to explore the use of this technology in future studies.

Subset Analysis and Ampligen Treatment

Dr. David Strayer, Medical Director at Hemipsherx Biopharma, described a retrospective study of the response to Ampligen in subjects who were positive or negative for XMRV. XMRV was tested at VIP Labs, which is associated with the Whittemore-Peterson Institute, and used similar techniques as those employed by Dr. Mikovits at the WPI.

In one study, serum from 208 subjects from a previous double blind placebo controlled Ampligen study were analyzed for XMRV. About one third were positive for the virus and two-thirds were not. Activity monitoring demonstrated less activity in XMRV+ subjects. That is, they were less active and presumably more ill.

Specifically, the improvement in exercise ability was monitored in these subjects. More improvement was measured inXMRV+ subjects than in XMRV- subjects. The table below describes the percentage of subjects who obtained at least 25% improvement in treadmill exercise duration at week 40 of treatment, as related to XMRV serology:

XMRV Status	Improved on Ampligen	Improved with placebo	Difference (AMP-PBO)
Pos (n=81)	44.7%	17.6%	27.1%
Neg (n=127)	34.0%	25.7%	8.3%
Overall (n=208)	39%	23%	15.9%

Dr. Strayer concluded that there was a 70% greater than average exercise response in XMRV+ subjects, and a 40% lower response in those who were XMRV-.

Medication use was monitored in all of these subjects as well. 53% of XMRV+ subjects were able to reduce their use of symptomatic medications, while only 32% of XMRV- subjects were able to reduce medication use.

These data suggest that subjects who are XMRV+ have an edge in responding to Ampligen, and that Ampligen may be a treatment for CFS.

Strayer reported plans by Hemispherx to monitor this in the current cost recovery (AMP-511) program, and hopefully to generate another large double blind placebo-controlled crossover study.

What Is Ampligen?

Ampligen is a poly-nucleic acid medication that has been studied for over two decades, but not yet FDA-approved for treating any disorder. It was found in the 1980's to be effective in treating Chronic Fatigue Syndrome symptoms, and subsequently underwent several trials in the US and abroad. Based on these results a new drug application was filed with the FDA in 2009, and in December of that year their Complete Letter of Response indicated that Ampligen was "approvable" but requested that more subjects be treated to assure safety and efficacy.

So far over 90,000 doses of Ampligen have been administered to over 900 subjects.

Ampligen has unique properties. It is **a selective Toll Receptor (TLR3) agonist with immunomodulatory, anti-proliferative, and anti-viral properties**.

The drug:

- Increases interferon a and b
- Restores TH2 immunity to the (more normal) TH1 type
- Activates the immune response (e.g., against HIV and renal carcinoma)
- Increases LAK and NK Cell activity
- Induces dendritic cell maturation (thus IgA and some IgG)
- Increases macrophage activity
- Restores delayed-type hypersensitivity
- Has antiviral effects versus retroviruses, HHV6, and RNA viruses.

This drug is administered intravenously twice weekly for at least 6 months. Side effects are mostly flu-like in nature, and **overall the drug has been tolerated extremely well**. While Ampligen is not considered a cure for CFS, published studies have demonstrated improvement in duration of exercise on a treadmill and a reduction in use of concomitant medications. **Actuarial studies suggest that Ampligen treatment saves about $5000 per year in medical expenses**. Dr. Lapp has been involved with Ampligen studies since 1988, and our personal experience at Hunter-Hopkins with the current AMP-511 study has been that **about one third of subjects achieve very significant global improvement**.

Ampligen is currently available only at Hunter-Hopkins and Dr. Peterson's Lake Tahoe clinic. Dr. Bateman's Fatigue Consultation Clinic in Salt Lake City will soon resume treatments, and Hemispherx is planning to add several other sites around the US, in addition to sites in Mexico and Argentina.

For more information check out
our website www.drlapp.net > Research > Ampligen),
Clinical Trials (phttp://clinicaltrials.gov > search for study NCT00215813),
and the Hemispherx Biopharma website at www.hemispherx.net.

For application to the AMP-511 Cost Recovery Study, contact our research coordinator, Wendy Fallick, at 704 5439692.

Because AMP-511 is a treatment protocol and not a drug study, insurance may cover some or all of the expenses involved.

We owe a great debt of gratitude to **Dr. William Carter** and Hemispherx Biopharma for developing Ampligen – the only proposed treatment for CFS – and supporting **research in CFS for over 22 years**. I know that Dr. Carter, his colleagues, and his company have experienced the same kind of humiliation and disdain that all of us involved with CFS have experienced, and it is a testament to their **courage and determination** that they have endured all these years when they could have abandoned CFS for more lucrative areas.

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