



The Path to a Cure Interview with MS virologist Steven Jacobson

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For decades, scientists have been looking for “the virus that causes MS.” Finding such a virus would be a great accomplishment – one that could then lead directly to treatment or prevention of MS based on blocking the virus. Despite extensive efforts, however, so far no such virus has been found. That doesn’t necessarily mean that viruses aren’t involved in MS. It might just mean that we need to change how we go about looking for them.

In the second of a series of interviews with scientists doing groundbreaking work in MS, Boston Cure Project’s Hollie Schmidt talks with virologist Steven Jacobson of the National Institutes of Health about how the search for viruses in MS is evolving. Steve is Chief of the Viral Immunology Section in the National Institute of Neurological Disorders and Stroke at the NIH and a member of the Boston Cure Project’s Scientific Advisory Board. His investigations have resulted in many important discoveries concerning the potential role of human herpes virus 6 (HHV-6) in MS. In this interview, Steve shares his perspectives on the search for MS viruses, the evidence implicating HHV-6 as a trigger of MS, and the new experiments he’s conducting to determine HHV-6’s role in this disease.

At the Boston Cure Project, our mission is to find out what causes MS. So we’re very interested in your work in exploring viral triggers of neurological diseases such as MS. Could you describe your approach?

First of all, those two words – “cause” and “trigger” – are very different and important to define. For a very long time, in many autoimmune diseases, everyone’s been looking for the “cause” of the disease, using a model that says if you get the virus it causes your disease. An example of this model is HIV – if you get HIV, you will go down the path of developing AIDS, and conversely if you don’t get HIV, you won’t get AIDS. That’s a pretty causative agent. The same is true for smallpox and polio – they’re both clearly causes.

So for years we’ve been trying to find the “MS virus,” a virus that causes MS. In fact we’ve all failed. I don’t think there is a single virus that causes MS, but there may be multiple “triggers,” which are common combinations of factors that we all get, but only certain people get sick and others don’t. For instance, you might get a cold that nobody else in your house catches. If everyone else in your house was similarly exposed to the virus, why did you get sick and they didn’t? This is exactly the type of thing we’re trying to understand with respect to MS.

This multiple trigger model is actually a much more typical model for disease than the single cause model, and it's the new model of medicine that we're focusing on. It's caused a shift in our way of thinking, not just in MS but in other diseases like diabetes, lupus, and heart disease. By the way, genetics research has shifted the same way – there will probably not be one MS gene but many MS genes, none of which on its own is sufficient to cause MS.

Given this shift toward finding triggers instead of causes, how does it change the way you conduct your research?

What we were trying to do in the past is look at a piece of tissue and see what the person with MS has that the non-MS person doesn't have. And that has really been hard to show. One interpretation is that there is nothing that's unique to MS. Another interpretation is that we see many things in people with MS but we also see them in people without MS. The challenge in that case is how to find out what is associated with MS. Our way of thinking is that, instead of looking for one agent that causes MS, we should try to find a combination of factors that's different in MS patients compared with a control group, and that's what led us to look at human herpes virus 6.

How did HHV-6 first become a candidate for triggering MS?

The interest in HHV-6 was initially sparked by a great study by Peter Challoner and his colleagues in 1995. They did exactly what I told you wouldn't work: they took MS brain material and subtracted the DNA sequences found in that material from those found in non-MS material, with the idea that whatever was left over would be unique for MS. What was really cool and different about that study is that it was an unbiased search – they weren't specifying in advance what they were looking for, like measles virus. Whatever sequence came out of that subtraction was what they were interested in finding. Anyway, what they found in one of the MS samples in addition to human DNA was a sequence for a human herpes virus. Now this virus had been recently discovered and not much was known about it. To their credit, this group didn't just stop there but instead labeled MS brains and non-MS control brains with monoclonal antibodies to the virus. Sure enough the MS brains lit up as if there was virus present, and it did not light up, at least to the same extent, in the control brains. That caught everyone's attention!

We were asked to reproduce this, but rather than doing more studies with brain samples, we decided to first look at peripheral blood for antibody responses to HHV-6. Now HHV-6 is a common virus and we all get exposed to it. Its best-known effect is the childhood illness roseola, which is basically a high fever followed by a rash. Anyway, 95% of us if not more will have been exposed to this virus whether we got the rash and fever as a child or

not. And since we've all been exposed to the virus, we will all have a certain class of antibodies against it, called IgG, which our body keeps on hand in case we encounter the virus again. Now there's another class of antibody, called IgM, which our bodies produce in an immediate response to something we've just encountered, whether it's something brand-new or something we've already seen in the past. We thought that perhaps we'd see a difference in IgM between people with MS and people without MS, so we worked with a group in California that developed an assay for IgM. We analyzed a number of our serum specimens, and sure enough the MS patients had significantly higher IgM antibodies to HHV-6 than the controls did. Both patients and controls had IgG, so if we just looked at that we would not have seen a difference. The IgMs told me there was a difference. And we got a paper published in *Nature Medicine* on our results.

What was the main significance of the IgM results?

Well, those results provided an initial form of independent verification and gave us reason to keep looking at this virus. We believe that using one technology to look at one system is not sufficient to explain what's going on in a disease. You've got to have molecular, immunological, pathological, clinical data to make your case. Just looking at antibodies would not be enough. Just looking for virus in the brain would not be enough. We have to combine it all. And that's where our research is going. For example, antibodies have been a major reason why so many viruses have been associated with MS. If you look for increased measles antibodies in people with MS, you'll see them. If you look for increased antibodies to some coronavirus, you'll see them. That's due to a dysregulation in the immune system in MS that produces more antibodies, and they are always IgG. Very rarely do you find IgM. So the fact that the HHV-6 response in MS was IgM was especially intriguing.

Next we looked at T cell responses to HHV-6, which is the other arm of the immune system, and wrote about that. Then we started taking a molecular approach to analyze HHV-6's involvement in MS. Working with groups in Italy and Baltimore, we used a very sensitive technique called PCR to amplify the HHV-6 nucleic acid sequences using serum, a component of the blood stream. We found that about 25-30% of people with MS had HHV-6 sequences in their serum, but we never found those sequences in non-MS subjects. One interesting thing this technique lets us do is detect different variants of the virus. HHV-6B is the variant that causes roseola, but the variant in the MS subjects was HHV-6A, which has been associated with the central nervous system. See how the picture is coming together?

So when you say we've all been exposed to HHV-6, is that HHV-6A or HHV-6B, or do we not know?

There are no good assays to distinguish between those two yet, so that's another important area to investigate, whether there are antibodies specific to 6A or 6B. And therefore we don't know the distribution of either variant. We also don't know much about the tropism of the virus, which is where it tends to reside in the body. HHV-6B is very T-cell tropic, it lives in lymphocytes, and 75-80% of us have HHV-6B in our lymphocytes. We find it in cellular material like peripheral blood and saliva with no difference between MS and non-MS subjects. HHV-6A, on the other hand, was found in non-cellular material, like serum and urine. This virus has been reported to be neurotropic, in other words, it resides in the nervous system. That's due to some remarkable studies based in Rochester, New York, where cerebral spinal fluid was collected from about 3,000 children who came to the emergency room with high fevers and seizures that may be related to roseola. When these samples were analyzed, the 6A variant was commonly seen, which gives us the idea that 6A might be neurotropic.

What was the next step for you after investigating HHV-6 using antibodies, T cells and DNA sequences in serum?

To me the icing on the cake is that finally we got back to the MS brain, because you need to study the tissue that is affected. The reason we study serum or blood is that these are systems we can access. That doesn't mean they're the best systems to study, they're just what you can actually get. Often times what we find in these samples may essentially even be surrogates of something else that's going on. One of the problems in being an MS researcher is how do we study the nervous system in a living patient? That's one of our major challenges and why it's so important for people to arrange to donate their brains to brain banks after they die. Of course the downside of that is that you generally get brains from older people who may have had MS for several decades and the events triggering it took place a long time ago. But that's certainly better than nothing!

So we went back and started looking at the MS brains we had, collaborating with a great neuropathologist in Canada, Sam Ludwin. Still looking for differences at the molecular level, we examined material from MS brain, including MS plaque and normal-appearing white matter, compared to control brains which all looked fairly normal. Sure enough we found more virus in the MS plaque than we did in the non-MS plaque.

That's the basic story on HHV-6 so far. There are lots and lots of nuances throughout all this, but that's the foundation of what we know right now based on our experimental data.

This sounds pretty straightforward, but it seems like the search for HHV-6 in MS overall is not as clear-cut – people are using so many different methods and

techniques and often coming up with contradictory results. Can you comment on that?

Yes, and this is further complicated by the virus being so difficult to work with. But science isn't based on consensus and doesn't require agreement to move forward. The classic example of this is ulcers which almost everyone thought were caused by stress. One guy says he thinks they're caused by bacteria, but nobody believes him. Sure enough he was right – ulcers are caused by *Helicobacter pylori*. And now plenty of people have reproduced it. Part of the problem with reproducibility of HHV-6 results is that there's a vicious circle involved. Up until now, HHV-6 hasn't been considered a really important disease virus. Let's face it, roseola is not a major concern, and therefore the tools are not available to study the virus to make associations with the disease. In a critical disease, people will work on standardizing their methods, but this virus has not been shown as critical, so people are coming up with their own methods, using different tissue, coming up with different results. Hopefully everything will get sorted out in time. For example, the IgM data is pretty convincing. We just published the ability to detect the virus in the brain. Another group from Rochester came to virtually the same conclusion. Two different groups, using two different patient samples, and different technologies, have come up with the same conclusion. So there are really exciting opportunities.

Now that there's enough evidence to reasonably suspect HHV-6 is somehow associated with MS, what are the next steps?

How do you move from association to causation? This is tough. I think one of the most important slides in the talks that I give has four words: "Association is not Causation," Just because something is there doesn't mean it's making you ill. So after years and years of associative work, now we can move onto mechanistic work. By the way, I wouldn't do any kind of mechanistic study if there was no association. If HHV-6 is looking like it has something to do with MS, only then does it become interesting to study. And if the association is there, then I'm going to study the mechanism. I'm not going to go into the mechanism if it has nothing to do with MS.

Some of the questions to explore include if the virus is in the brain, what cells is it infecting in the brain? How does the virus get into the cell, how does it get out of the cell? What is the immune response to the virus? Does the immune response to the virus have something to do with the disease? Is there a resemblance between the virus and our own proteins which would lead to an autoimmunity hypothesis involving molecular mimicry and things like that? Since we've found positive results, the onus is on us to explain why it's there.

I think that probably the only way using today's technologies to nail down whether HHV-6 is a trigger for MS is to do a clinical trial of an antiviral drug in people with MS. That will tell us a lot if we get a positive result. If we get a negative result, there might be many explanations, such as that we used the wrong antiviral. We may not find that HHV-6 is *the* trigger of MS, but it may be a trigger for a subset of patients, and we want to define that subset. So in the study we would find a subset of MS subjects that has the virus, give them a drug, monitor them to see whether the drug reduces that virus, and then see whether they get better in terms of their clinical disease.

Is there a specific antiviral you have in mind that would work against HHV-6?

We have several antivirals in mind. Again there's a vicious circle at work. The antivirals available for HHV-6 are not that good. They're actually better for other viruses within the family. For instance, acyclovir is good for herpes simplex but not at all good for HHV-6. Probably one of the best drugs against HHV-6 is foscarnet, but it's a very toxic drug. I'm not sure I'd want to give that to an MS patient. There's another drug called valganciclovir which also has HHV-6 activity. It may not be the best, but it is a very safe drug.

Your other main focus is on the retrovirus human T-cell lymphotropic virus type 1 (HTLV-1). Have you gained any insights from this research that apply to MS?

We're gaining many insights into MS mechanisms and treatment from working with this virus. It causes a disease called HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM-TSP), a chronic progressive neurologic disease that is clinically similar if not identical to the primary progressive form of MS. HTLV-1 is related to HIV but is very different from HHV-6. Compared with HHV-6, which basically infects everyone, a lot fewer people are affected with HTLV-1, but that's still about 40 million. Of those 40 million, a subset go onto develop HAM-TSP. Anyway, we've been studying that disease with the same questions as we have for MS, such as how can this virus that affects 40 million people cause disease only in a subset of individuals? In the case of HAM-TSP, the evidence for association with HTLV-1 is very strong and we feel that the disease may be caused by an immune response against the virus when it gets expressed in the brain and spinal cord.

There are many benefits to studying MS and HAM-TSP at the same time. Using HAM-TSP, we're studying a chronic neurological disease with a known viral agent to find a mechanism in MS, a disease that is clinically similar but whose agent is unknown. Conversely, we can take any of the therapies we have for MS and try them in HAM-TSP. We're currently doing a trial with Avonex. We're also working with a new drug called Zenopax (a human monoclonal antibody) and have published results on using that in HAM-TSP. That is now in clinical trial in MS with very promising results.

Back to doing a clinical trial to demonstrate the involvement of HHV-6, what if the virus operates by a hit and run model where the initial infection sets off a destructive disease process, but after that point the virus is still present but not causing any harm?

The goal is to get MS patients involved as early as possible. With someone who's had MS for many years, maybe the initial triggers have already happened and are no longer present or relevant. We've done some work with patients with relapsing remitting disease showing that it's easier to find HHV-6 during exacerbation than during remission. That supports the idea that HHV-6 is involved in the disease process throughout. But the point's a good one, MS patients may have different things going on at different points on the timeline. You'll notice that all of the MS therapies except maybe the experimental remyelination therapies are aimed at treating the patient early on. You may also know that one of the great boons to MS, interferon beta, was originally tried as an antiviral to interfere with virus replication. The mode of action of interferons are not known, but it's conceivable that it's working as an antiviral against a virus that's still active.

Could interferon beta be counteracting HHV-6 specifically?

We have some evidence that there's a reduction in HHV-6 in some of the interferon therapies. The study didn't reach statistical significance but the numbers were pretty low. This is another avenue to pursue.

What specific MS-related experiments are you working on right now?

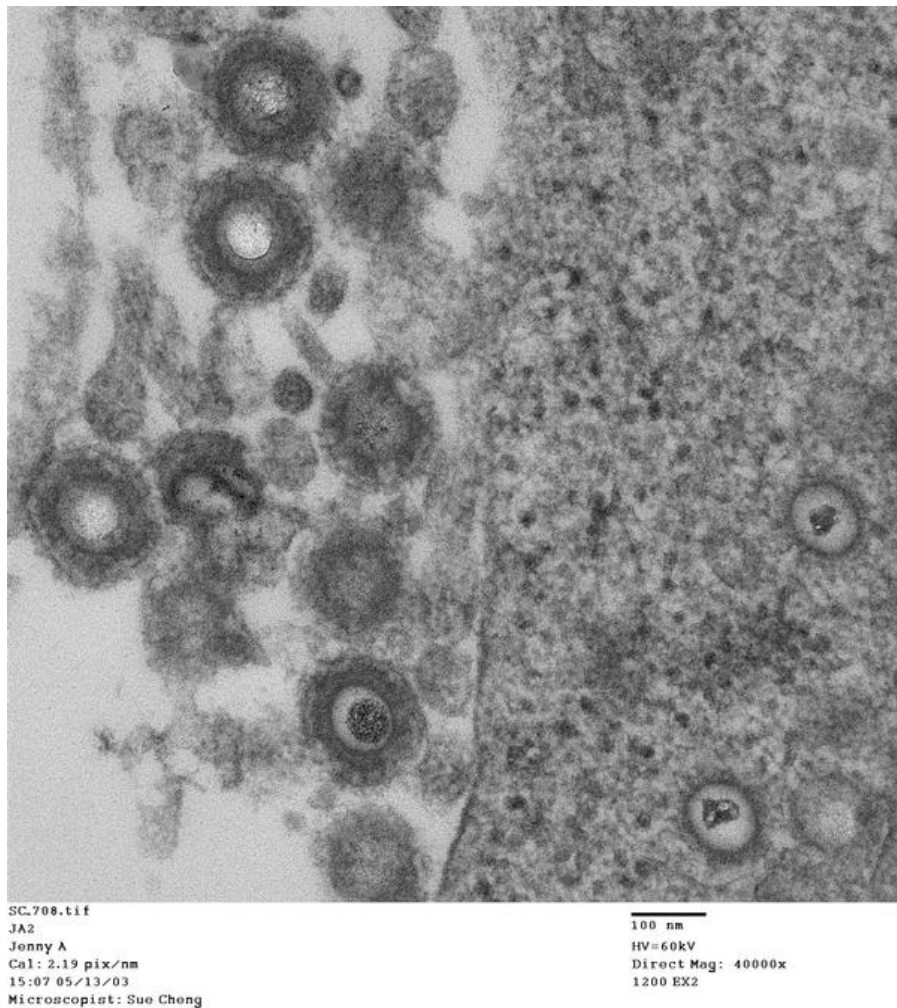
Our main interest overall is in finding the mechanism of how HHV-6 might trigger MS. We're still continuing on how to make better "diagnostics" or methods of finding HHV-6, because that's an area that needs to be improved. We're looking into the extent of infection of virus in the brain, where is it, what cells does it infect, and what is it doing. There's evidence that HHV-6 infects the oligodendrocyte and/or the astrocyte, in which case we'd want to know if it could kill these cells or alter their function. And we're working on one fascinating autoimmunity hypothesis that comes out of cytomegalovirus (CMV) literature. HHV-6 and CMV are enveloped viruses, so when they leave a cell to infect another cell, they wrap themselves in a bit of the cell's membrane. Perhaps when the immune system is roused to attack the virus, it also attacks the proteins from the host cell, which might have been an oligodendrocyte. And therefore the other oligodendrocytes in the area with those same proteins are likewise targeted, so they suffer from guilt by association. Those are some of the angles we're trying to explore.

As for the antiviral clinical trial I mentioned, we've contacted a couple of drug companies and have begun writing protocols. We'd like it to be a multicenter

trial, and are hoping that it could be off and running within the year. I'm still not fully satisfied with our means for detecting the virus, which we need to do in this trial, but otherwise we're very ready to do something with this. Hopefully we can parlay this into something useful for patients.

Is there anything else you'd like our readers to know?

Keep on supporting MS research! I'd also like everyone to know that at the NIH here we have a very large MS group here funded by taxpayer money. For the past 25 years, the US government has made a very sincere and committed effort to study this disease, which is a good use of taxpayer dollars! When you vote, vote appropriately, and remember that we take our mandate seriously. We're doing the people's work, not some ivory tower type of thing, and we're thankful for everyone who supports it.



Human herpes virus 6 (round objects) infecting T cell (darker area, right)
Photo: Jenny Alqvist and Susan Cheng