Interview

Dr Leslie Weiner speaks to Charlotte Barker, Commissioning Editor

Leslie P Weiner
University of Southern California, Los Angeles, CA, USA
lweiner@usc.edu

Leslie P Weiner, MD, is Professor of Neurology and Molecular Microbiology and Immunology at the Keck School of Medicine of the University of Southern California (USC). He also holds the Richard Angus Grant, Sr Chair in Neurology. He received his BA at Wilkes College (PA, USA) and an MD from the University of Cincinnati College of Medicine (OH, USA). He completed his internship at the State University of New York in Syracuse (NY, USA) and residency at The Johns Hopkins Hospital in Baltimore (MD, USA). He completed two fellowships: Medicine (Neurology) and Epidemiology at the The Johns Hopkins University School of Medicine, and Immunology at the NIH Laboratory of Slow Virus Infections, NINDS at Laurel (MD, USA). He was Associate Professor of Neurology at Johns Hopkins University before he moved to the USC School of Medicine in 1975 as Professor of Neurology and Microbiology. He was appointed Chairman of the Department of Neurology in 1979 and served until 2003. Dr Weiner is actively involved in both laboratory and clinical research related to viral infections of the nervous system, autoimmune disorders, gene therapy and, of late, stem cells. Multiple sclerosis is his main area of interest. He has just completed a study of a T-cell vaccine in secondary progressive multiple sclerosis. Dr Weiner serves or has served on numerous scientific committees, such as the John Douglas French Foundation for Alzheimer's Disease, Starbright Foundation, Hereditary Disease Foundation, Amyotrophic Lateral Sclerosis Society of America and the National Multiple Sclerosis Society. He has served on many NIH review committees. He is currently a member of the Research Programs Advisory Committee of the National Multiple Sclerosis Society, and a Director of the USC Center Without Walls of the Nancy Davis Race to Erase MS.

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What attracted you to working on multiple sclerosis? In what areas is your current research focused?

I have been interested in immunology since I was an undergraduate and wrote a paper on hayfever immune responses. However, my medical school thesis was on the genetics of multiple sclerosis (MS), and at that stage I became intrigued by the pathology and immunology of the disease, as well as the fact that we knew so little about it.

At the moment, we are working in two main areas. First is cell-based gene therapy, and second is stem cell therapy. We have also conducted some work in T-cell vaccination, but that is currently not ongoing.

You have had success in treating a mouse model of MS using gene-therapy approaches: can you tell me a bit more about this work?

We have engineered a retrovirus, already licensed in the USA and in use in several diseases, and made it into a cassette. We then engineered a gene, in this case a myelin gene, so that the peptide would be secreted over 24 h. The purpose of that, as allergists have been doing for years with foreign proteins (e.g., bee stings, hayfever and so on), is to induce low-dose tolerance, in this case to a self protein. We think this is, from a conceptual point of view, a very realistic way of inducing tolerance to myelin protein, which we believe to be one of the immunodominant epitopes in MS. Other antigens may well be involved, but we have shown in our work that low-dose tolerance to one antigen causes suppression of many other antigens.

However, in considering moving to human studies, we had some concerns with simply incorporating the gene into the patient's own cells. If we used, for example, human fibroblasts, we would

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have to biopsy the patient, grow the cells, insert the gene construct and inject the cells into the patient. That would really be a boutique operation, plus if something were to go wrong we would not be able to locate the cells and remove them. So our next step was to develop a chamber for the cells. This prevents the immune system attacking the cells, but allows the flow of nutrients in and peptides out of the cell. The chamber is implanted just under the skin. There are several advantages to this system: it is easy to use, it only needs to be applied once per year, the same cells can be used for all patients, and if something were to go wrong we can simply remove the chamber.

The biggest issue is that we need to prove that this will work in a human – we have not yet started human work, although we have the human cells, which have been approved by the NIH, and the virus construct, which has been approved by the RNA Advisory Committee of the NIH. Safety is always an issue with any novel therapeutic approach. Before we begin human trials, which we think we are ready to do, we need to carry out certain safety tests. For example, the US FDA wants us to find out what will happen to the gene if the transfected cells die. We have a number of requests for government and venture capital funds to finance further work towards the clinic.

There are other gene therapies that are currently being tested; for example, we have been involved with the Bayhill gene-therapy program, which involves injecting DNA in a plasmid construct. This showed some immunologic activity in a Phase I trial and few adverse effects, and is now entering a Phase II/III trial to investigate the efficacy. This is essentially the same principle of low-dose tolerance. My only concern is that this could affect every cell in the body, whereas the approach we have developed retains the DNA in a localized area.

What do you think are the major hurdles for clinical translation of gene therapy for MS?

Gene therapy has a bad reputation at the moment, as a young person died during a trial of gene therapy for a rare genetic condition at the University of Pennsylvania (PA, USA). That trial had some major flaws in how patients were selected, the informed consent procedures and how patients were monitored. My feeling is that we need to have increasingly safe vectors (lentiviruses and herpesviruses) that are not going to give us the reactions we have seen with previous gene therapy. However, viral vectors are improving day-by-day, and I am very optimistic that we can correct these flaws. I am optimistic that eventually all types of gene therapy will be in clinical use.

Recently, you have been working with stem cells to determine their role in brain repair. What should be the priorities in determining the potential of stem cells in the regeneration of damaged tissue in MS?

We are based in California, USA, which of course has a major stem cell program, and we are working with embryonic stem cells. We are mostly focusing on embryonic-derived stem cells, but we also use cells from baby teeth, which I get from my grandchildren! We are working on various problems of differentiation and survival that we think need to be solved before we can start work in humans.

There are two major safety priorities that must be addressed before stem cell therapy can be considered for clinical use. First, we need to have cell lines that have been cultured without any animal component (e.g., mouse feeder layers). Second, they must be very pure, with no possibility of a neoplastic transformation. Cancer is a big worry in stem cell therapy; there must not be any cells that are pluripotential. There is still the potential for transdifferentiation or, if the culture is not pure enough, primitive cells being injected by accident. There is evidence that brain tumors, particularly glioblastomas, are triggered by stem cells.

In addition, we currently have no way to track cells once we have injected them into patients. Where the cells migrate to and whether they will be effective are still difficult to assess. Therefore, the imaging and tracking techniques in humans need

a lot of work. Then we can track a transplanted cell within a living patient and determine if it reached its target. This work is progressing.

In terms of efficacy, there are, in fact, endogenous stem cells in the CNS of MS patients that gather around the MS lesions, but do not function to repair them. Therefore, there is the question of whether transplanted cells are going to be more successful than endogenous stem cells. We think that they will act differently, but they may require some engineering to deal with the inflammatory response and inhibitors present after the destruction of myelin. There is evidence that in the CNS of MS patients, owing to this destruction of myelin, factors are being released that inhibit repair. Therefore, we need to take into account inhibitory factors and inflammation, and ensure that the transplanted cells are able to function despite these. The CNS environment in a MS patient is hostile so we have to overcome that. I feel that we are getting close to that in both *in vitro* and *in vivo* studies and in the next few years, if we can assure the public that there will be no tumor formation or other safety issues, this will be ready for a clinical trial.

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Do you think the demyelinating disorders are particularly suited to cell-based therapies?

Many people think not, but I disagree. The diffuseness of the lesions and the fact that there are endogenous stem cells already present in MS that show little activity are the reasons why many scientists think that MS is not a good target for cell therapy. But I feel that all these factors can be overcome with modern technology.

Neural stem cells injected into animal models will migrate towards areas of damage, so there probably will not be a problem in getting the cells into the right areas. The inflammatory response is a double-edged sword: inflammation can inhibit repair responses and yet some inflammation is thought to be necessary for repair. Cell-based therapies will require some immunosuppression in order for the cells to survive, but complete immunosuppression is likely to be counterproductive and prevent repair. Gene therapy might be a solution in that it may allow selective immunosuppression, suppressing factors that we think are harmful, while sparing those thought to be necessary for repair.

You mentioned that you have currently suspended your work on T-cell vaccination: can you tell me a bit more about that? Do you hope to restart the work?

Basically, our initial T-cell vaccination studies did not work. We are confident that we know where we went wrong, but at the moment we do not have the finances to make corrections and do another trial. However, we are hopeful that other groups will be more successful.

Overall, I feel that this is an approach that has not been fully explored. We conducted a sound Phase I/II study, but the vaccine did not show efficacy. The reasons for that are complex. The vaccine itself may not have been good enough, but, in addition, we used very sick patients with severe disease. A significant number of patients receiving the vaccine did improve, but so did the placebo group: over 2–3 years of the study, few of the placebo group had progression of their disease, and there was no significant difference between treatment and placebo groups. There is a company, Opexa (TX, USA), that is developing a T-cell vaccine along very similar lines to our study.

What do you think are the most promising potential therapeutic strategies for the future?

My concept of MS is that it is a disease of T-cell regulation. I believe that people can be genetically susceptible to MS but that it is not a genetic disease. There are viruses involved, but it is not an infectious disease. Therefore, if one really wants to cure this disease, one has to interfere with the

abnormalities of regulation. My own feeling is that gene therapy has the greatest chance of being able to affect these complex pathways. Stem cells are a potential option, but they will only be valuable if they are able to interact with endogenous stem cells, and there are significant hurdles. All treatment options will need to be applied early in the disease course, before significant damage to the axons has occurred, because there is nothing on the horizon with the ability to repair axons.

Do you expect to see a cure for MS in your lifetime?

I do expect to see a cure for MS in my lifetime. The amount of progress in the last 15 years has been unbelievable to me. As someone who took care of MS patients at a time before there were any treatments, I can tell you it is incredible how well these patients are doing now that we have the six licensed and off-label drugs. The thing I am most concerned about is that we might have a cure for the disease, but that patients and societies will not be able to afford it. Even now we have patients who cannot access existing therapies because they live in remote areas, do not have the right insurance, or simply cannot afford the very high prices that pharmaceutical companies are charging for these drugs.

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