**July 2015 Update for PRP/Matristem Therapy & Advocacy Efforts by US Institute for Advanced Sinus Care and Research**

Dear ENS Community,

We have had a lot of promising advances in our efforts to understand/prevent/cure ENS. Attached is an update of our efforts.

**1. How have the results of PRP/Matristem therapy been progressing?**

Since we began employing PRP/Matristem therapy, we have treated 132 patients from 17 countries. Of these, 111 or 84% of patients have reported an improvement in their symptoms, 13 patients (10%) have not reported any followup, 5 patients (5%) have reported no improvement at all, and 3 patients (2%) have reported getting worse after therapy. Of the 111 who have reported an improvement, I would say that 17 have reported a dramatic/life changing benefit, 83 have reported a moderate or significant benefit, and 11 have reported only a mild benefit. Of the 3 patients who have reported getting worse, they have reported that their ENS symptoms have been getting worse, such as the paradoxical obstruction and/or the pain or burning in their nose is worse. I have not been able to tell if this is do to the injections or just a result of the progression of their symptoms. I have had 1 patient who said that their mouth dryness got worse after an injection, but they reported an improvement in ENS symptoms with the injection and stated that they had preexisting mouth dryness. I have now seen visible turbinate regrowth in an estimated 20-30 patients from endoscopy. Number of injections have ranged from 1 to 11 injections. I believe that each injection is providing an additive benefit, and I have not noticed that the timing of the injections is very important. Overall, I am very encouraged and now confident that this therapy is working and helping the majority of my patients. I plan to present these data at a tissue reengineering conference in the near future and I am now working to create a protocol for a randomized, blinded, placebo-controlled crossover study to provide level IB evidence that this therapy is helpful, and will begin fundraising for such study. This study will be expensive, costing about $10,000 for IRB review, approximately $75,000 for treatment materials, and probably $15,000 for study coordination/logistics. So, overall, I will need to raise probably $100,000 to fund a study for 40 patients.

**2. How did the ARS Summer Symposium go?**

The American Rhinologic Society holds an annual course in Chicago each year, where we teach ENTs about current advances in sinus surgery. This year, the course became free for all ARS members and we had record attendance with an additional 90 ENTs present. During one panel, James Palmer discussed to the entire audience that his biggest fear was creating Empty Nose Syndrome. I was invited to moderate the panel on Socioeconomic Changes in Sinus Surgery, and I invited Eric Holbrook, a rhinologist from Harvard Medical School and Chair of our Ethics Panel to present. He warned against performing unnecessary surgery and non-indicated surgery, and discussed for example, not performing turbinate reductions during a septoplasty when they were not needed. Also, another one of my panelists, Stephanie Shintani-Smith, discussed abandoning outfracture, resection, and/or cautery of the turbinates and instead only performing submucous resections when indicated. David Poetker also presented a panel on nasal and turbinate surgery of which Jayakar Nayak was a panelist, and he discussed his

experience with the cotton test, his surgical technique and results with Alloderm implants (which I do not like) and his growing population of ENS patients. I also participated in that discussion and discussed my experience with PRP/Acell. Encouragingly, the panel 100% agreed that ENS was a real issue that warranted further study and was a dreaded complication to be avoided. Many panelists and audience members discussed their theories as to why a small percentage of patients develop ENS after turbinate surgery. Devyani Lal, a sinus cancer surgeon, discussed many valid reasons why sinus cancer patients might not develop ENS but patients selected for turbinate reductions might go on to develop ENS. Overall, there was a significant focus on ENS at this meeting that was not present at other meetings and absolutely no discussion was had that this is simply a psychiatric disease that is not related to the surgery. I met separately with Jayakar Nayak during the meeting and had a nice discussion and we will further collaborate on our ENS patients in the future. I do not like Alloderm as I have not seen good results in my several years of trying it; I believe it worsens ENS from the eventual scar formation that results and a recent meta-analysis in the Laryngoscope showed only 21% benefit), however, Jayakar has had some good results with it with some patients "progressing from an F to a B". I recommend patients who want Alloderm to now consider seeing Jayakar instead of Stephen Houser (both are good friends who I respect tremendously) because Jayakar is working on a prospective trial examining the results of implants and will publish these data in the future. Jayakar and I will likely try to have dinner together in Dallas in September and increase our coordination of ENS efforts.

**3. How did your meeting with Pradeep Mahajan go?**

Over the summer, Dr. Pradeep Mahajan, an internationally respected stem-cell researcher presented as a keynote speaker to The Ohio States annual course on Tissue Regeneration. I took Dr. Mahajan out for dinner and spent four hours with him discussing stem-cell therapy for chronic sinus disease and ENS. He validated the Acell/PRP technique and stated that is was likely to be one of the most successful approaches for ENS because it contained both enriched platelets (greater than 2 million/mL of activated platelets are essential for initiating a wound regeneration response, and the Matristem contained ECM, which is also essential. ECM can be obtained from bladder, intestinal sources, and other areas which are likely to be effective. My technique likely requires circulating stem cells to become activated by the PRP/Acell, which is not as much of a problem in turbinates, because turbinates are engorged in blood and receive 20% of the circulating blood volume. However, it can be a problem in areas of dense scarring. Also, my technique is likely to have no risk of developing cancer, as it requires normal functioning stem cells to come from the blood, whereas enriching or transforming stem cells in a petri dish with growth factors or other therapies run a small risk of developing a cancer. We discussed methods to better activate platelets from my PRP. I explored the use of calcium chloride and thrombin but rejected both due to the risk of tissue necrosis and developing an autoimmune reaction to a critical circulating protein. Instead I am now mechanically agitating our platelets for an additional 5 minutes and injecting them through a bent needle which likely mechanically activates them. Also premixing platelets with the collagen found in Acell activates them, and is likely why PRP/ACell is working so much better than other therapies. Based on my discussion with Dr. Mahajan, I have now abandoned either delivering PRP alone or delivering Acell alone, as both by themselves are unlikely to work from a theoretical approach.

**4. How are your stem-cell therapies progressing?**

I have tried PRL/PRP/Acell sheeting delivered via surgery for several patients including those with chronic sinus disease. I have had mixed results. These have been some of my toughest patients with the most severe forms of sinus disease or ENS, but I have not noticed the impressive regrowth of tissue compared to some that I am seeing from multiple PRP/Acell injections. I have several theories on this. One is that many patients with ENS likely have a connective tissue disorder, or fragile nerves, etc, and surgery is intrinsically harmful to them and they do not recover well from surgery. So the act of surgery and cutting into their turbinate remnants might be harmful in itself for these patients. Two, the use of PRP/ACell might be acting like a tissue expander (a technique plastic surgeons use to grow more scalp after cancer, for example) and the hydrostatic pressure expands the turbinate remnant and new healthy tissue grows into the space. With surgery, I am unable to mechanically expand a space with hydrostatic pressure since I cut into it so much. In any case, PRP/Acell is exceeding my expectations more often than PRL/PRP/Acell has delivered via surgery. Dr. Mahajan stated that bone induction should be easier with PRP/Acell compared to blood vessel induction. As a result, I am intentionally scraping bone during my injections with PRP/Acell hoping to stimulate some BMP hormone release and bone growth.

**5. What is in the future for your ENS efforts?**

I will be going to spend a day with a leading orthopaedic stem cell doctor near St. Louis Missouri in October 2015 to learn their technique for bone marrow and fat aspirates. I will hopefully present next year our ENS efforts at the leading stem cell conference in the US and hopefully meet new researchers and contacts there. Hopefully, we will begin fundraising and slowly raise the $100,000 to support a high quality trial of PRP/Acell and publish this. After that is completed, we will then present this paper to all of the leading insurance companies and try to get them to cover this therapy with medical insurance.

Overall, I am pleased with the progress we are making. We still have much work to do.

Best wishes,
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