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Intravenous SONG-modulated laser-activated allogeneic cord blood mesenchymal stem cells for the treatment of end-stage heart failure: a preliminary clinical study

T. Ovokaitys[1], A. Paronyan[2], H. Hayrapetyan[3], P. Hollands[4]

[1]CEO, Qigenix, Carlsbad, CA, USA
[2]Cardiologist, Erebouni Medical Center, Yerevan, Armenia
[3]Head of Erebouni Cardiology Center, Yerevan, Armenia
[4]CTO, Qigenix, Carlsbad, CA, USA

Corresponding Author: Todd Ovokaitys, MD; e-mail: drtodd@gematria.com

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Abstract

Objective: **This preliminary clinical study assessed the potential use of Strachan-Ovokaitys Node Generator (SONG)-modulated laser-treated expanded (3-5 passages) cord blood Mesenchymal Stem Cells (MSCs) in the treatment of end-stage heart failure.**

Patients and Methods: **Ten patients were enrolled into the study, each with a Left Ventricular Ejection Fraction (LVEF) of ≥20% and ≤25%. Allogeneic expanded cord blood MSCs were treated with a SONG-modulated laser prior to intravenous infusion at a total dose of 100 x10^6 MSCs per patient. All patients also received 5 minutes of SONG-modulated laser light to the anterior precordial region and 5 minutes to the left lateral chest. The LVEF of each patient was assessed using echocardiography on Days 3, 7, 31, 62 and 93 post-treatment.**

Results: **All patients showed an increase in LVEF following SONG-modulated laser-treated expanded MSC treatment and remained with increased LVEF for at least 3 months. Two patients in the study subsequently died of heart failure.**

Conclusions: **This is the first description of the use of SONG-modulated laser-treated cord blood MSCs in the treatment of end-stage heart failure and it sets the groundwork for future double-blind randomised controlled clinical trials.**

Introduction

According to the World Health Organization (WHO), end-stage heart failure (HF) results in approximately 17.9 million deaths per year[1]. In the UK alone in 2004 coronary heart disease cost the health service £29.1 billion[2]. The only currently known curative treatment option for these patients is Orthotopic Heart Transplant (OHT) and many of these patients often have to resort to relying on a Left Ventricular Assistance Device (LVAD) whilst awaiting transplant. Many patients with HF die before a suitable heart donor becomes available[3] with the expected 1-year survival rate of patients with severe HF agreed to be 30%[4].

The effect of SONG-modulated laser light on stem cells has been studied previously with confirmation that the SONG-modulated laser light interacts with human Very Small Embryonic Like (hVSEL) stem cells in Platelet Rich Plasma (PRP) to induce proliferation[5]. A theoretical model for the mode of action of SONG-modulated hVSEL stem cells has been proposed utilising theory from quantum physics[6]. The hVSEL stem cells are pluripotent and therefore have considerable potential in the regeneration of damaged organs even before any intervention using SONG-modulated laser light[7]. The small size (1-4 μm in diameter) of hVSEL stem cells gives them the added advantage that they can cross the blood-brain barrier and do not become trapped in the various capillary beds when administered intravenously.

MSCs are known to be multipotent stem cells and therefore are thought to have considerable potential in regenerative medicine[8]. The use of MSCs in the treat-

ment of HF has been reported by several groups with a consensus that MSC treatment can be effective in terms of improving prognosis and exercise capacity[9]. It has been proposed that MSCs secrete various cytokines, adhesion molecules and chemokines which may activate endogenous cell repair and that the replacement of endogenous cells by MSCs is unlikely[10]. In addition, multipotent MSCs have a low expression of class II major histocompatibility complex (Class II MHC) making them an ideal choice for allogeneic cell therapy procedures[11]. It has also been shown in mice that MSCs, when administered intravenously, become trapped in the pulmonary capillary bed[12]. Mice treated with sodium nitroprusside showed decreased levels of pulmonary MSC trapping, but these technologies have not been tested in humans. There have been reports of intracardiac MSC treatment in humans for cardiomyopathy, where the MSC were delivered using cardiac catheter technology[13]. This technology proved to have some benefit, although it is an invasive approach and much more research is needed to assess its short-term and long-term safety and efficacy. In view of the above, we conducted a clinical study to assess the potential use of Strachan-Ovokaitys Node Generator (SONG)-modulated laser-treated expanded (3-5 passages) cord blood MSCs in the treatment of end-stage HF.

Patients and Methods

Patients

All patients in this clinical study were male (n=10). The age range was 51-68 years. Each patient provided informed consent to take part in the clinical study. Informed consent was taken by the Cardiology staff at Erebouni Medical Center (Yerevan, Armenia). The risk-benefit profile for this group of patients was considered favourable based on clinical judgement.

The patient exclusion criteria were any co-morbidities beyond hypertension and ischaemic cardiomyopathy.

The baseline Left Ventricular Ejection Fraction (LVEF) was assessed prior to treatment on Day 0 by using echocardiography (Siemens Acuson SC2000).

A medical history was collected for each patient before the study, and this was supplemented by the notes and observations of the cardiologists who were treating the patients. The patients all suffered from typical ischaemic and hypertensive congestive HF, with LVEF ranging from 20% to 25%. Participants were all in severe end-stage HF and could all be considered as heart transplant candidates.

Mesenchymal Stem Cells (MSCs)

Allogeneic clinical grade expanded cord blood derived MSCs (passaged 3-5 times) were obtained from Invitrx Therapeutics (Lake Forest, CA, USA). The frozen cord blood-derived MSCs were flown to Armenia for use in the clinical study and were thawed rapidly in a 37°C water bath, washed and prepared for use. The total MSC cell count per patient prior to SONG-modulated laser treatment was 100 x10^6 viable cells. Each patient received SONG-modulated laser treated expanded cord blood MSCs from a single donor. No Human Leucocyte Antigen (HLA) typing was carried out.

The SONG-modulated laser

This was a 670 nm 5 mW (Sanyo, Osaka, Japan) SONG-modulated laser with the SONG set at 60% optical phase conjugation (OPC) for a resultant beam power of 1 mW.

SONG stands for Strachan-Ovokaitys Node Generator and was developed by the first author of this paper in collaboration with his physicist colleague Scott Strachan. SONG modulation of the laser cancels the central wavelength band of the laser output in a process described as non-fringing destructive interference.

The remaining upper and lower wavelength bands create a beat frequency pattern of sparse nodes of constructive interference which represents the physical visible light that remains.

Modulation of this complex wave form pattern results in a rapid traverse of these nodes that can reach pulse repetition frequencies at intervals as rapid as less than a femtosecond. The destructive interference and sparseness of the nodes reduces the flare at the surface of the tissue interface. This decreases both the reflectiveness of photons which have entered a zone that has just experienced a photon absorption as well as the related scattering effect. The depth of penetration of sparse nodes may be 10-20 times that of ordinary photons at the surface of an interface such as human skin.

Laser Activation of expanded cord blood MSCs and administration to patients

The frozen expanded (passaged 3-5 times) cord blood MSCs were rapidly thawed in a 37°C water bath, washed and suspended in 10 mL of sterile normal saline (SteriCare Solutions, Halmon City, TX, USA).

MSCs were then exposed to the SONG-modulated laser (as described above) for a total time of 3 minutes. The SONG-modulated laser-treated cord blood MSCs were then immediately administered to the patient intravenously at a total dose of 100 x10^6 MSCs per patient at a rate of 5 mL/minute. All patients were monitored for any adverse reactions.

SONG-modulated laser guidance

Immediately following the intravenous administration of SONG-modulated MSCs, each patient received SONG-modulated laser guidance to the cardiothoracic region. All patients received 5 minutes of SONG-modulated laser light to the anterior precordial region and 5 minutes to the left lateral chest.

Supplement administration to patients

All patients received Complete Aminos (Gematria, Carlsbad, CA, USA) supplements in the period following treatment with SONG-modulated laser activated MSCs. Complete Aminos contains DL-Phenylalanine, L-Lysine, L-Valine, L-Leucine, L-Isoleucine, L-Methionine, L-Threonine, L-Glycine, L-Glutamine, L-Glutamic Acid, L-Arginine, L-Ornithine, L-Serine, L-Alanine, L-Aspartic Acid, L-Histidine, L-Proline, L-Cystine, L-Taurine and L-Citrulline. Patients were given 2 g per day of Complete Aminos supplement for 30 days following SONG-modulated laser-activated MSC treatment.

Post-treatment patient assessment

Following intravenous administration of SONG-modulated laser-activated cord blood MSCs (Day 0), each patient was assessed for LVEF using echocardiography on Day 3, Day 7, Day 31, Day 62 and Day 93 post-treatment. Basic observations (temperature, heart rate and blood pressure) remained in the normal range for all patients at the time of treatment and at subsequent follow-up appointments. All patients were assessed for creatinine, complete blood count (CBC), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and estimated glomerular filtration rate (eGFR). This blood was taken pre-treatment and at each echocardiography follow-up appointment.

Statistical analysis

All results are expressed as mean±standard deviation (SD) values. A Student's *t*-test was used where appropriate. Correlation analysis between various parameters was performed using Pearson correlation. For all comparisons, a p-value<0.05 was considered as statistically significant.

Results

All 10 patients in this clinical study (carried out in 2015) benefitted from SONG-modulated laser-activated MSC infusions in terms of their LVEF assessments (Table 1 and Figure 1). No patients suffered any

Table 1. Mean LVEF changes (Δ LVEF) after SONG-modulated laser-activated MSC therapy in patients with end-stage HF monitored during a follow-up period of 93 days. All patients were males. Abbreviations: HF, heart failure; LVEF, Left Ventricular Ejection Fraction; MSC, Mesenchymal Stem Cells; n/a, not applicable; SD, standard deviation; SONG, Strachan-Ovokaitys Node Generator.

	Day 0	Day 3	Day 7	Day 31	Day 62	Day 93
Patient 1 – Age: 59 years	20%	25%	28%	31%	32%	32%
Patient 2 – Age: 66 years	25%	no data available	28%	33%	33%	44%
Patient 3 – Age: 68 years	20%	30%	32%	34%	37%	43%
Patient 4 – Age: 59 years	23%	23%	27%	22%	no data available	29%
Patient 5 – Age: 65 years	20%	20%	22%	24%	24%	27%
Patient 6 – Age: 54 years	20%	23%	23%	24%	27%	28%
Patient 7 – Age: 53 years	20%	23%	23%	23%	23%	23%
Patient 8 – Age: 63 years	23%	25%	26%	27%	30%	32%
Patient 9 – Age: 51 years	20%	23%	23%	25%	27%	25%
Patient 10 – Age: 67 years	22%	23%	25%	25%	25%	25%
Mean	21	24	26	27	29	31
SD	1.99	2.56	3	4.1	4.4	7
Mean Δ LVEF	n/a	2.44	1.55	1.1	1.33	2.33
***p*-value**	**n/a**	**0.009**	**0.0008**	**0.001**	**0.0004**	**0.0008**

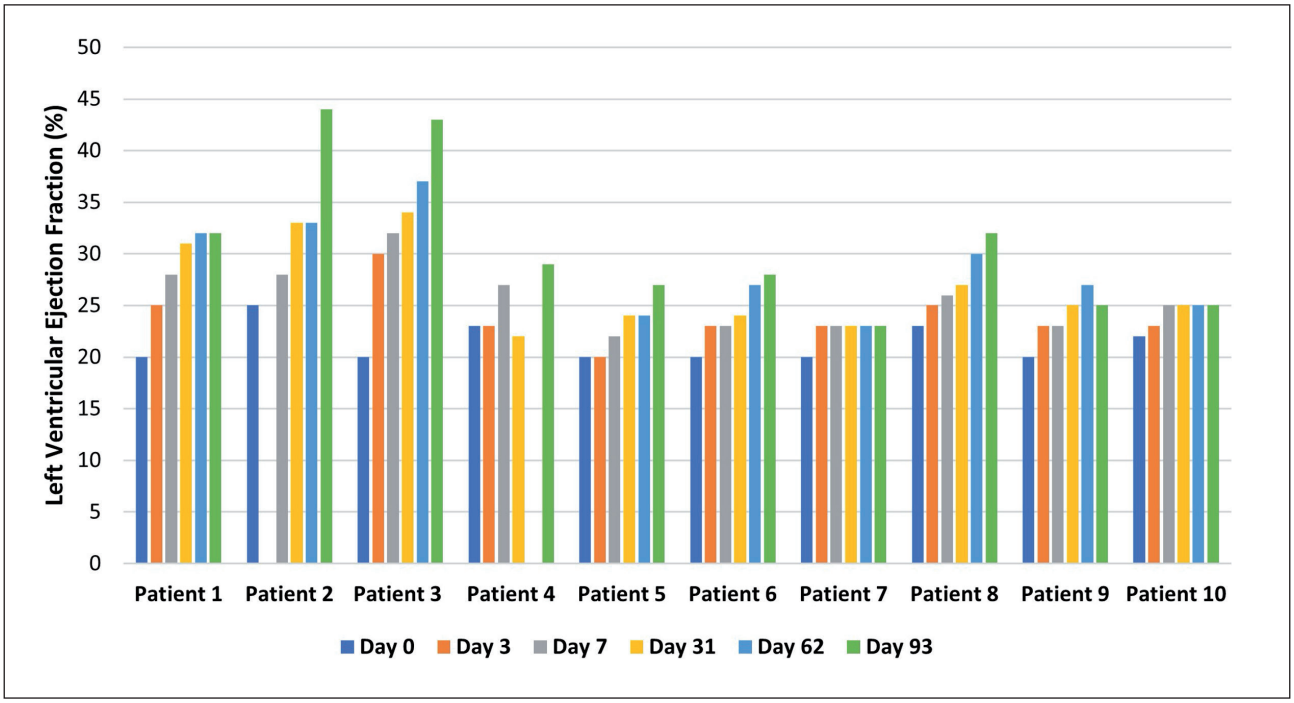

Figure 1. Histogram of mean left ventricular ejection fraction (LVEF) changes after SONG-modulated laser-activated MSC therapy in patients with end-stage heart failure monitored during a follow-up period of 93 days. All patients were males.

adverse reactions to the SONG-modulated laser-activated MSC treatment. Two patients (patients 7 and 10) died from HF after the completion of the clinical study. One patient (Patient 8) developed a suspected mild reaction to the supplements given as part of the treatment, which were discontinued immediately. The symptoms resolved and no further supplements were prescribed for this patient.

Patient 1 (age: 59 years)

This patient had a baseline LVEF before treatment of 20%. On Day 3 following treatment his LVEF had increased to 25%, on Day 7 his LVEF increased to 28%, on Day 31 his LVEF increased to 31%, on Day 62 his LVEF was 32% and on Day 93 his LVEF was 32%. The overall percentage improvement in LVEF in this patient was +12%. The patient remains stable and well at the time of writing.

Patient 2 (age: 66 years)

This patient had a baseline LVEF before treatment of 25%. On Day 3 following treatment his LVEF was not assessed, on Day 7 his LVEF increased to 28%, on Day 31 his LVEF increased to 33%, on Day 62 his LVEF was 33% and on Day 93 his LVEF was 44%. The overall percentage improvement in LVEF in this patient was +19%. The patient remains stable and well at the time of writing.

Patient 3 (age: 68 years)

This patient had a baseline LVEF before treatment of 20%. On Day 3 following treatment his LVEF had increased to 30%, on Day 7 his LVEF increased to 32%, on Day 31 his LVEF increased to 34%, on Day 62 his LVEF was 37% and on Day 93 his LVEF was 43%. The overall percentage improvement in LVEF in this patient was +23%. The patient remains stable and well at the time of writing.

Patient 4 (age: 59 years)

This patient had a baseline LVEF before treatment of 23%. On Day 3 following treatment his LVEF remained at 23%, on Day 7 his LVEF increased to 27%, on Day 31 his LVEF decreased to 22%, on Day 62 his LVEF was not assessed and on Day 93 his LVEF was 29%. The overall percentage improvement in LVEF in this patient was +6%. The patient remains stable and well at the time of writing.

Patient 5 (age: 65 years)

This patient had a baseline LVEF before treatment of 20%. On Day 3 following treatment his LVEF remained

at 20%, on Day 7 his LVEF increased to 22%, on Day 31 his LVEF increased to 24%, on Day 62 his LVEF was 24% and on Day 93 his LVEF was 27%. The overall percentage improvement in LVEF in this patient was +7%. The patient remains stable and well at the time of writing.

Patient 6 (age: 54 years)

This patient had a baseline LVEF before treatment of 20%. On Day 3 following treatment his LVEF had increased to 23%, on Day 7 his LVEF remained at 23%, on Day 31 his LVEF increased to 24%, on Day 62 his LVEF was 27% and on Day 93 his LVEF was 28%. The overall percentage improvement in LVEF in this patient was +8%. The patient remains stable and well at the time of writing.

Patient 7 (age: 53 years)

This patient had a baseline LVEF before treatment of 20%. On Day 3 following treatment his LVEF had increased to 23%, on Day 7 his LVEF remained at 23%, on Day 31 his LVEF remained at 23%, on Day 62 his LVEF remained at 23% and on Day 93 his LVEF remained at 23%. The overall percentage improvement in LVEF in this patient was +3%. The patient has since died.

Patient 8 (age: 63 years)

This patient had a baseline LVEF before treatment of 23%. On Day 3 following treatment his LVEF had increased to 25%, on Day 7 his LVEF increased to 26%, on Day 31 his LVEF increased to 27%, on Day 62 his LVEF increased to 30% and on Day 93 his LVEF increased to 32%. The overall percentage improvement in LVEF in this patient was +9%. The patient remains stable and well at the time of writing.

Patient 9 (age: 51 years)

This patient had a baseline LVEF before treatment of 20%. On Day 3 following treatment his LVEF had increased to 23%, on Day 7 his LVEF remained at 23%, on Day 31 his LVEF increased to 25%, on Day 62 his LVEF was 27% and on Day 93 his LVEF was 25%. The overall percentage improvement in LVEF in this patient was +5%. The patient remains stable and well at the time of writing.

Patient 10 (age: 67 years)

This patient had a baseline LVEF before treatment of 22%. On Day 3 following treatment his LVEF had increased to 23%, on Day 7 his LVEF increased to 25%, on Day 31 his LVEF remained at 25%, on Day 62 his LVEF remained at 25% and on Day 93 his LVEF remained at 25%. The overall percentage improvement in LVEF in this patient was +3%. The patient has since died.

Blood analysis

CBC, Creatinine, AST, ALT and eGFR all remained in the normal range from the point of treatment to final follow up.

LVEF changes during the follow-up period

The p-values for mean LVEF changes (mean Δ LVEF) compared to the baseline LVEF values were statistically significant at all timepoints ($p<0.05$; Table 1).

Discussion

This is the first description of the potential safety and efficacy of SONG-modulated laser-treated, expanded (passaged 3-5 times) allogeneic cord blood MSCs to treat end-stage HF. The study has limitations in terms of the number of participants (n=10), the fact that there were no control subjects in the study receiving standard current treatment and that there was no double-blind protocol or randomisation in the study[14]. Despite these limitations, which can be addressed in future double-blind randomised controlled clinical trials, this study shows the clear potential of SONG-modulated laser-treated cord blood MSCs to increase the LVEF in patients with end-stage HF. The improvement in LVEF following SONG-modulated laser-treated cord blood MSCs was statistically significant in all 10 patients treated. This technology can improve the LVEF in patients waiting for a heart transplant and may even remove the need for a transplant in some patients. It is proposed that it is the SONG-modulated laser treatment which appears to enhance the efficacy of MSCs in this study. Two patients (patient 7 and patient 10), who showed the weakest response to SONG-modulated laser-treated MSCs, have subsequently died. In these poor responders, there may be a rationale for repeated treatments (beyond the single treatment in this study) to raise the LVEF to levels associated with improved prognosis. The other 8 patients in the clinical study who showed higher levels of LVEF post-treatment remain well at the time of writing and have not needed to proceed to heart transplantation.

Meta-analysis of using non-lasered MSCs to treat HF produced data which suggested that such non-lasered MSC interventions did not have any significant

impact on cardiovascular death, myocardial infarction, HF, and overall death[15]. There are many variables in the quality, viability and efficacy of MSCs which can be derived from many different sources, thus making standardisation difficult[16]. This may be one reason why these non-lasered studies produce variable results with no overall benefit to the patients. In contrast, when the SONG-modulated lasered MSCs were used in this study to treat HF, it resulted in all 10 (100%) of the patients benefitting during the clinical study in terms of an increased LVEF. It should be noted that 2 patients (20%) subsequently died from HF, but these deaths occurred after the completion of the clinical study. Eight of the patients (80%) remain alive and well at the time of writing. Compared to an expected 30% 1-year survival rate in HF, 80% survival after 6 years in this study suggests the potential of a significant reduction of morbidity and mortality related to end-stage HF.

The actual mode of action of SONG-modulated laser light on stem cells is still being researched, although it appears that by considering the potential interactions at the quantum level (as discussed in the introduction) this may result in a deeper understanding not only of this mechanism but also in the overall improved understanding of health and disease[6].

It has previously been described that combination stem cell therapy may be effective in the treatment of congestive HF[17]. The rationale here is that the use of multiple stem cell types (e.g., bone marrow MSCs and CD34+ haemopoietic stem cells together) may be more effective in the repair of the deficient stem cell niche and reduced stem cell numbers often seen in the disease. This may be because both MSCs and CD34+ haemopoietic stem cells (HSCs) are multipotent and in combination their combined capabilities, and therefore overall efficacy, may be increased. Preparations of both of these cell types (MSCs and HSCs) are also highly likely to contain increased numbers of hVSEL stem cells[18] which may contribute significantly to the apparent increase in efficacy.

More recent unpublished work in this area by Ovokaitys et al has shown the safety and efficacy of SONG-modulated laser-treated autologous hVSEL stem cells in PRP in the treatment of HF. The advantages here are that the hVSEL stem cells used are autologous and therefore easily obtained and that hVSEL stem cells are pluripotent. Results from such treatments using SONG-modulated laser-treated autologous hVSEL stem cells to treat HF include a 61-year-old male with a LVEF of 18% awaiting a heart transplant. The prognosis was 30% survival at 1 year without treatment. The first treatment for this patient used SONG-modulated laser-treated allogeneic-expanded cord blood MSCs as in the clinical study above in 2015. Subsequently, he received annual treatment using SONG-modulated laser-treated autologous hVSEL stem cells and his LVEF has stayed between 38% and 40%.

A second patient had severe HF with a LVEF 25%-30%. He was 66-year-old at the time of his SONG-modulated laser-treated autologous hVSEL procedure in April 2017. In August 2017 his follow-up echocardiogram showed a LVEF of 50%-55%. In late 2017 he was able to stop all of his cardiovascular and anti-hypertensive medications including ramipril, carvedilol, low-dose aspirin and clopidogrel. In December 2013 (prior to the autologous hVSEL stem cell procedure) he had an Implantable Cardioverter-Defibrillator (ICD) inserted, which has remained in place but will be removed when the battery charge runs out at his next cardiologist visit. He remains alive and well and is not taking any medications related to HF. The most recent LVEF was 45%. These are, of course, single isolated cases with no double-blinding or controls but nevertheless the benefits seen are tantalizing and much more basic and clinical data are needed to confirm these observations.

Recent work has shown that hVSEL stem cells can be isolated from many tissues of the body, suggesting a much more complex role for hVSEL stem cells in normal physiology and disease than was previously thought[19,20]. The presence of hVSEL stem cells has recently been shown in human heart tissue in both healthy and ischaemic hearts and across a wide age range[21]. These hVSEL stem cells may be contributing to homeostasis within the tissue and may be additionally recruited in disease states[22]. The intravenous infusion of hVSEL stem cells concentrated in PRP with laser activation using a SONG-modulated laser in HF, as described above, is therefore supported by previous observations. The novel factor in this work is the SONG-modulated laser activation of the hVSEL stem cells which seems to give the hVSEL stem cells renewed "vigour" to seek and repair damaged tissue. The application of the SONG-modulated laser light to the patient is based on the hypothesis that the SONG-modulated laser light may enhance hVSEL engraftment in tissues which have received SONG-modulated laser light. This hypothesis is the subject of ongoing research but those patients who receive SONG-modulated laser light to the anatom-

ical areas where the hVSEL stem cells are needed do seem to do better than those patients who receive no SONG-modulated light to their affected areas.

In this study, expanded cord blood allogeneic MSCs were selected as the target for SONG-modulated laser activation. The rationale for this choice was based on literature evidence that MSCs are naturally capable of producing osteocytes, chondrocytes, myocytes and adipocytes[23]. It is also known that MSCs can produce a wide range of growth factors and cytokines which may reflect in their immunomodulatory and regenerative properties[24], along with MSC-derived exosomes which may be contributing a cell-free mechanism to the overall process of regeneration[25]. This is the basic concept of regenerative medicine where stem cells are proposed to replace damaged somatic cells.

In contrast, hVSEL stem cells in PRP are pluripotent and as such may be acting in a different and perhaps more effective way to MSCs, especially following laser activation. Our proposition is based on the fact that both disease[26] and ageing[27] can be correlated to a reduction in endogenous stem cells and to a degradation of the stem cell niche[28]. The number of stem cells available has also been shown to decline in paediatric heart disease[29], along with the suggestion that autologous supplementation of the stem cell niche may be beneficial. In the patient suffering from HF, it is therefore safe to assume that as part of the disease process endogenous stem cell numbers have decreased and the stem cell niche has been degraded or damaged. When the underlying problems are reduced stem cell numbers and a damaged stem cell niche, the direct regeneration of cardiac somatic cells by exogenous stem cells of any source is likely only to have a transient benefit to the patient since the underlying condition persists.

Our hypothesis views regenerative medicine in a different way and may be reflected in the astonishing benefits we have seen across a wide range of diseases (unpublished data) when patients receive SONG-modulated laser-activated hVSEL stem cells in PRP. Firstly, hVSEL stem cells are pluripotent and can in theory produce any tissue including cardiomyocytes. Nevertheless, and much more importantly, hVSEL stem cells could directly replenish the decreased endogenous stem cell reserve and stem cell niche in disease, thus facilitating a long-term benefit to patients. This is the concept of endogenous stem cell regeneration, not differentiated somatic cell repair. The SONG-modulated laser-treated hVSEL stem cells may also be capable of repairing the components of the stem cell niche, thus re-enabling the long-term survival of existing endogenous stem cells and new cardiac stem cells derived from exogenous hVSEL stem cells. Secondly, PRP is a concentrated and complex mixture of cytokines and growth factors which certainly has the potential to enhance the process of stem cell niche repair[30]. Thirdly, PRP contains large numbers of platelets which produce various biologically active molecules through the secretion of alpha granules[31]. Fourthly, induced pluripotent stem cell-derived cardiomyocytes are known to be capable of secreting exosomes which contribute to myocardial repair[32]. It is therefore likely that exosomes, produced by hVSEL stem cells, contribute to the regenerative effect seen. All of these components of PRP are exposed to SONG-modulated laser light which may enhance the properties of each component. Hence, much more basic research is needed in this area. Clear interactions of SONG-modulated laser light with hVSEL stem cells in PRP have already been shown[5]. We believe that the use of SONG-modulated laser-activated autologous hVSEL stem cells in PRP to treat a wide range of disease is a much more powerful combination than MSCs either in clinical grade culture media or normal saline. Our preliminary data in this publication supports this concept. Our overall hypothesis agrees with other authors who state that hVSEL stem cells regenerate, whereas MSCs rejuvenate[33].

At present, the work on SONG-modulated laser-activated hVSEL stem cells in PRP has been on autologous venous blood collected to produce PRP. This is a quick and easy process which seems effective for most patients. Nevertheless, the resultant autologous hVSEL stem cells may have undergone changes due to ageing and may even be suboptimal for the purpose of stem cell niche repair in some patients. A possible solution, which needs further research, is to assess both young healthy adult donor blood and umbilical cord blood as an allogeneic source of PRP for MSC proliferation[34], with subsequent SONG-modulated laser activation. Such an approach may result in increased clinical efficacy because of the young biological age of the hVSEL stem cells in young healthy young adult blood and umbilical cord blood PRP. The likely increased levels of platelets and cytokines/growth factors may also be important in overall efficacy. Such an improved efficacy would have to be balanced by the increased cost and complexity of producing and banking allogeneic young healthy adult blood and umbilical cord blood PRP. Nevertheless, either healthy young adult blood donors or um-

bilical cord blood may be the perfect source of PRP for allogeneic SONG-modulated laser treatment and the effort may be worthwhile. Such allogeneic PRP would have to undergo infectious disease screening and ABO Rh typing prior to use.

Conclusions

There is still a lot of work to be done to fully understand the biological and clinical benefits of SONG-modulated laser treatment of stem cells. There are clearly beneficial effects when MSCs receive SONG-modulated laser treatment and are used to treat HF. Nonetheless, it is becoming increasingly clear that autologous hVSEL stem cells in PRP are very easy to obtain and seem to have the perfect properties to respond to SONG modulated laser light. They also have a potential clinical mechanism, whereby pluripotent hVSEL stem cells restore multipotent tissue specific stem cell numbers lost to ageing or disease in depleted areas and restore the multipotent stem cell niche. This provides a true regeneration process which repopulates and repairs the stem cell niche which in turn enables ongoing repair and replacement of diseased somatic cells. The long-term cure of disease is at the heart of regenerative medicine and SONG-modulated laser autologous or allogeneic hVSEL stem cells may be the optimal, safe and effective route to this goal.

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Author Contributions:

Todd Ovokaitys: Composing and revising the manuscript, funding of the work, clinical study
design, data analysis, manuscript revision and joint final approval of the manuscript for publication.
Aramais Paronyan: Composing and revising manuscript, funding of the work, clinical study design, data analysis, manuscript revision and joint final approval of manuscript for publication.
Hamlet Haryapetyan: Composing and revising manuscript, funding of the work, clinical study design, data analysis, manuscript revision and joint final approval of manuscript for publication.
Peter Hollands: Composing and revising manuscript, data acquisition analysis and interpretation and joint final approval of manuscript for publication.

Ethical Approval:

The clinical study protocol was reviewed and approved by the Ethics Committee of the Department of Cardiology (Erebouni Medical Center, Yerevan, Armenia) for safety and risk-benefit analysis. Each patient provided informed consent to take part in the clinical study.

ORCID:

Todd Ovokaitys: https://orcid.org/0000-0002-1565-5996
Aramais Paronyan: https://orcid.org/0000-0002-6870-4616
Hamlet Haryapetyan: https://orcid.org/0000-0002-8764-5623
Peter Hollands: https://orcid.org/0000-0003-4116-1954

Conflict of Interest:

Dr. Ovokaitys is CEO of Qigenix. Professor Hollands is CTO of Qigenix. Dr. Paronyan and Dr. Haryapetyan have no conflict of interest to disclose.

Data Availability Statement:

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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