

# SCIENCE TELEGRAM

## MTS Spark Wave® Publications

2<sup>nd</sup> Semester 2020

**Chen et al., 2019:**

**Modulation of VEGF and MAPK-related pathway involved in extracorporeal shockwave therapy accelerate diabetic wound healing: Modulation of VEGF pathway involved in ESWT accelerate wound healing**

*Department of Surgery, Division of Plastic Surgery, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan.  
Wound Repair Regen. 2019 Jan;27(1):69-79.*

Extracorporeal shockwave therapy (ESWT) has a significant positive effect to accelerate chronic wound healing. This study investigated whether the vascular endothelial growth factor (VEGF)-related pathway has involved in ESWT enhancement of diabetic wound healing. A dorsal skin defect (area, 6 × 5 cm) in a streptozotocin-induced diabetes rodent model was used. Thirty-two male Wistar rats were divided into four groups. Group I consisted of nondiabetic control; group II, diabetic control without treatment; group III, diabetic rats received ESWT; and group IV, rats received Avastin (a VEGF monoclonal antibody) on day 0 (post-wounding immediately) to day 7 and ESWT on day 3 and day 7. The wound healing was assessed clinically. The VEGF, endothelial nitric oxide synthase (eNOS), and Ki-67 were analyzed with immunohistochemical staining. The mRNA expression of mitogen-activated protein kinase-related genes was measured by real-time quantitative real-time polymerase chain reaction. The results revealed wound size was significantly reduced in the ESWT-treated rats as compared to the diabetic control ( $p < 0.01$ ). The positive effect of ESWT-increasing wound healing was significantly suppressed in pretreatment of the Avastin group. Histological findings revealed significant increase in neo-vessels in the ESWT group as compared to the control. In immunohistochemical stain, significant increases in VEGF, eNOS, and Ki-67 expressions were noted in the ESWT group as compared to that in controls. However, Avastin suppressed the shockwave effect and down-regulation of VEGF, eNOS, and Ki-67 expressions in the Avastin-ESWT group as compared to that in the ESWT alone group. We found that highly mRNA expression of Kras, Raf1, Mek1, Jnk, and Jun at early stage in the ESWT group, as compared to the diabetic control. These evidences indicated treatment with multiple sessions of ESWT significantly enhanced diabetic wound healing associated with increased neovascularization and tissue regeneration. The bio-mechanism of ESWT-enhanced wound healing is correlated with VEGF and mitogen-activated protein kinase-mediated pathway.

*CLINICAL RELEVANCE: Solid basic research on diabetic wound healing.*

*DEVICE: MTS orthowave180c, applicator CP155.*

**Chen et al. 2020:**

**Proteomic Analysis of Peri-Wounding Tissue Expressions in Extracorporeal Shock Wave Enhanced Diabetic Wound Healing in a Streptozotocin-Induced Diabetes Model**

*Division of Plastic Surgery, Department of Surgery, Kaohsiung Medical University Hospital, Kaohsiung 807, Taiwan.  
Int J Mol Sci. 2020 Jul 30;21(15):5445.*

Our former studies have demonstrated that extracorporeal shock wave therapy (ESWT) could enhance diabetic wound healing but the bio-mechanisms remain elusive. This study investigated the

changes of topical peri-wounding tissue expressions after ESWT in a rodent streptozotocin-induced diabetic wounding model by using the proteomic analysis and elucidated the molecular mechanism. Diabetic rats receiving ESWT, normal control, and diabetic rats receiving no therapy were analyzed. The spots of interest in proteome analysis were subjected to mass spectrometry to elucidate the peptide mass fingerprints. Protein expression was validated using immunohistochemical staining and related expression of genes were analyzed using real-time RT-PCR. The proteomic data showed a significantly higher abundance of hemopexin at day 3 of therapy but down-regulation at day 10 as compared to diabetic control. In contrast, the level of serine proteinase inhibitor (serpin) A3N expression was significantly decreased at day 3 therapy but expression was upregulated at day 10. Using real-time RT-PCR revealed that serpin-related EGFR-MAPK pathway was involved in ESWT enhanced diabetic wound healing. In summary, proteome analyses demonstrated the expression change of hemopexin and serpin with related MAPK signaling involved in ESWT-enhanced diabetic wound healing. Modulation of hemopexin and serpin related pathways are good strategies to promote wound healing.

*CLINICAL RELEVANCE: Solid basic research on diabetic wound healing.*

*DEVICE: MTS orthowave180c, applicator CP155.*

**Joos et al. 2020:**

**Low-Energy Extracorporeal Shockwave Therapy as a Therapeutic Option for Patients with a Secondary Late-Stage Fibro-Lymphedema After Breast Cancer Therapy: A Pilot Study**

*Department of Physical Medicine and Rehabilitation and UZ Brussels, Brussels, Belgium.*

*Lymphology Clinic & European Center of Lymphatic Surgery, UZ Brussels, Brussels, Belgium.*

Lymphat Res Biol. 2020 Aug 11.

**Background:** Secondary lymphedema (LE) can occur after breast cancer (BC) therapy with axillary lymph node surgery and/or radiotherapy. Reported incidence varies around 20%. The aim of this study was to see whether low-energy extracorporeal shockwave therapy (ESWT) is a therapeutic option in end-stage secondary upper limb fibro-LE.

**Methods and Results:** A pilot study was performed on 10 adult patients who presented with an end-stage LE after BC treatment. They were all treated with usual physical therapy and all had lymphatic surgery before. Eight sessions of ESWT were applied, 2600 shocks at 0.1 mJ/mm<sup>2</sup>, 2/week during 4 weeks. Upper limb volume decreased nonsignificantly, from 3086.4 ± 539.47 to 2909.1 ± 471.60 mL. Mean circumference of the upper limb was significantly decreased from 32.3 ± 3.01 to 31.4 ± 2.71 cm at the height of the upper arm, from 29.1 ± 2.89 to 28.1 ± 2.71 cm at the height of the elbow, and from 27.5 ± 4.08 to 26.8 ± 3.75 cm at the height of the forearm. Subjective measurements by visual analog scale showed significant decrease in both hardness from 57.3 ± 15.84 to 24.4 ± 21.89 mm and subjective feeling of edema from 44.2 ± 16.90 to 23.2 ± 21.16 mm. No adverse features were reported.

**Conclusion:** We added some evidence that low-energy ESWT is well supported and has additional benefits also in longstanding fibro-lipo-LE on swelling of the arm leading to more subjective comfort for the patients.

*CLINICAL RELEVANCE: Relatively new field of application - not many studies available yet.*

*DEVICE: MTS dermagold100, applicator OP155.*

**Gollmann-Tepeköylü et al., 2020:**

**Shock waves promote spinal cord repair via TLR3**

*Department of Cardiac Surgery and Division of Clinical and Functional Anatomy, Medical University of Innsbruck, Innsbruck, Austria.*

JCI Insight. 2020 Aug 6;5(15):134552.

Spinal cord injury (SCI) remains a devastating condition with poor prognosis and very limited treatment options. Affected patients are severely restricted in their daily activities. Shock wave therapy (SWT) has shown potent regenerative properties in bone fractures, wounds, and ischemic myocardium via activation of the innate immune receptor TLR3. Here, we report on the efficacy of SWT for regeneration of SCI. SWT improved motor function and decreased lesion size in WT but not Tlr3<sup>-/-</sup> mice via inhibition of neuronal degeneration and IL6-dependent recruitment and differentiation of neuronal progenitor cells. Both SWT and TLR3 stimulation enhanced neuronal sprouting and improved neuronal survival, even in human spinal cord cultures. We identified tlr3 as crucial enhancer of spinal cord regeneration in zebrafish. Our findings indicate that TLR3 signaling is involved in neuroprotection and spinal cord repair and suggest that TLR3 stimulation via SWT could become a potent regenerative treatment option.

*CLINICAL RELEVANCE: Current basic research parallel to the clinical spinal cord injury Neurowave study. Hot topic in SWT area.*

*DEVICE: MTS orthogold180c, applicator CG050.*

**Sagir et al., 2019:**

#### **Efficacy of Extracorporeal Shockwaves Therapy on Peripheral Nerve Regeneration**

*Nursing Department, Health College, Sinop University, Sinop.*

*Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Medeniyet University, Istanbul, Turkey.*

*J Craniofac Surg. Nov-Dec 2019;30(8):2635-2639.*

**Purpose:** This study was conducted to determine the effects of different doses and methods of extracorporeal shock wave treatment (ESWT) on the sciatic nerve regeneration of rat model using unbiased quantitative stereological techniques and to know which method and dose were effective.

**Methods:** Twenty-five Wistar albino rats were used in the experiment. All animals were randomly divided into 5 groups. To the first group (control, n = 5) ESWT and surgery were not applied. To 2nd group (E300\*2, n = 5), twice doses of 300 impulses uESWs (unfocused) were applied. To 3rd group (E500\*2, n = 5), twice doses of 500 impulses uESWs (unfocused) were applied. To 4th group (E300\*2, n = 5), twice doses of 300 impulses of fESWs (focused) were applied. To 5th group (E500\*2, n = 5), twice doses of 500 impulses of fESWs (focused) were applied. Rats were sacrificed and nerve samples analyzed on the 22nd day following the operation.

**Results:** There is a variable increase in the axon numbers among the shockwave treated groups in compare to the control group. The focused groups showed better improvement and the 300-focused group has shown the highest regeneration rate.

**Conclusion:** The authors found that ESWT promotes nerve regeneration, increases the thickness of the myelin sheath and that the most effective result is in the 300 shock wave.

*CLINICAL RELEVANCE: Regenerative medicine – Peripheral Nervous Sytem.*

*DEVICE: MTS orthogold100, focused applicator OE050.*

**Uloko et al., 2020**

#### **Novel Use of a Shock Wave Device for Energy Flux Density Threshold Testing of the Distal Ventral Erect Penile Shaft as a Marker of Penile Dysesthesia/Hypersensitivity Associated with Premature Ejaculation**

*San Diego Sexual Medicine.*

*21st Annual Fall Scientific Meeting of Sexual Medicine Society of North America (SMSNA), Abstract No.041*

**Introduction:** Premature ejaculation (PE) is the most common sexual dysfunction in men. Traditional PE management is based on pharmacologic strategies to increase/decrease central

inhibition/excitation, respectively. A subset of PE patients was identified with extreme penile hypersensitivity; simply touching the frenular region during sexual activity resulted inevitably in premature ejaculation. The clinical dilemma is that there are no objective and clinically relevant clinical tests of penile dysesthesia/hypersensitivity to successfully identify this subset of PE patients

**Objectives:** We herein describe, in a subset of men with PE, a novel biologic marker for penile dysesthesia/hypersensitivity.

**Methods:** Energy flux density is a measure of the energy per square area (mJ/mm<sup>2</sup>) released by a shockwave pulse at a specific location. The threshold of energy flux density tolerable to the patient was determined during pharmacologic penile erection. The UroGold 100 MTS OP155 parabolic probe, Hz 3 was applied to the right and left lateral mid-shaft, the dorsal mid-shaft, the proximal ventral shaft and the distal ventral shaft overlying the frenulum. At each location, the patient was asked if there was pain on a 4-point scale (0 none, 1 mild, 2 moderate, 3 severe). We started with energy flux density values of 0.05 mJ/mm<sup>2</sup> and increased to a maximum of 0.14 mJ/mm<sup>2</sup>, if tolerable. Energy flux density threshold was defined as the energy flux density when the patient experienced a 2-3 pain level. In those who demonstrated peri-frenular penile dysesthesia/hypersensitivity, the extent of the dysesthesia was mapped, the region was numbed (penile anesthesia test) and the patient was asked to masturbate in a private setting, usually in the office, to determine ejaculation latency.

**Results:** 51 men without PE (mean age 48 +/- 15, IELT > 5 min) and 14 men with PE (IELT < 1 min) (mean age 25 +/- 7) were studied during pharmacologic penile erection. In men without PE, the energy flux density threshold in all erect penile locations was 0.12 - 0.14 mJ/mm<sup>2</sup>. In the 14 men with PE, the energy flux density threshold in the distal erect ventral shaft region was significantly lower at 0.05 - 0.07 mJ/mm<sup>2</sup>, while all other erect penile locations yielded threshold values similar to men without PE (0.12 - 0.14 mJ/mm<sup>2</sup>). 9 patients underwent penile anesthesia testing and IELT values during masturbation increased to over 10 minutes. Figure 1 depicts the novel use of erect penile shockwave energy flux density testing as a diagnostic marker in this subset of men with PE.

**Conclusion:** Energy flux density threshold may be the first objective, sensitive, clinically relevant biologic marker to identify men whose PE is a result of a localized penile dysesthesia/hypersensitivity in the peri-frenular region. Identification of this subset of PE patients could lead to alternative strategies to cure their PE.

### Penile Energy Flux Density testing



*CLINICAL RELEVANCE: An Emerging Indication for Shockwave Therapy. There are no major clinical experience reports on this topic in the field yet. SWT could be used for both diagnosis and treatment of PE. PE is highly prevalent.*

*DEVICE: MTS urogold100, unfocused applicator OP155.*

Yih et al., 2020:

**Lumbo-Sacral Low Intensity Shock Wave Therapy for Persistent Genital Arousal Disorder/Genito-Pelvic Dysesthesia Using the UroGold 100 MTS**

*San Diego Sexual Medicine.*

21st Annual Fall Scientific Meeting of Sexual Medicine Society of Nort America (SMSNA), Abstract No.134

**Introduction:** Low intensity shockwave therapy (LiSWT) was introduced to sexual medicine in 2010 as penile shockwave therapy for the non-invasive, non-hormonal, non-pharmacologic treatment of erectile dysfunction. Ever since, sexual medicine clinicians have been broadening LiSWT utilization for bothersome sexual health concerns. LiSWT has been shown to be anti-inflammatory to such processes as radiculitis and researching Pubmed for LiWST treatments of various pain conditions yields over 600 citations. Persistent genital arousal disorder (PGAD) a form of genito-pelvic dysesthesia (GPD), is a sexual medicine condition highly associated with despair, emotional lability, catastrophization and suicidality.

**Objective:** The objective of this chart review was to examine outcomes of a specific population of women with distressing PGAD/GPD suspected to be from radiculopathy of the sacral spinal nerve roots who underwent lumbo-sacral LiSWT.

**Methods:** Patients with PGAD/GPD suspected to be from radiculopathy of the sacral spinal nerve roots have the following: i) abnormal neuro-genital testing, ii) abnormal lumbo-sacral MRI with degenerative disc disease, herniated nucleus pulposus, annular tear, facet cyst, and/or Tarlov cyst; and iv) consultation with a spine surgeon. Patients were selected for lumbo-sacral LiSWT who had distressing symptoms of PGAD/GPD with unrelenting, unprovoked feelings of arousal, pain or other dysesthesia > 3 mo, who had either had minimally invasive spine surgery (MISS) without full resolution of symptoms; had not been considered a candidate for MISS, or had chosen not to have lumbosacral surgery. Treatment involved using the UroGold 100 MTS, OP155 parabolic probe, Hz 3, energy density 0.06 - 0.10 mJ/mm<sup>2</sup> for 2-4 treatments, with 2100 - 4200 shocks to the left and right sacral and/or lumbar regions depending on the suspected site of pathology based on the MRI. The Patient Global Impression of Improvement (PGI-I) was administered at the second treatment visit and thereafter.

**Results:** Thirteen women (mean age 38 +/- 11 years) with various symptoms of PGAD/GPD were identified. 7 had MISS with improvement but not full resolution of their distressing symptoms and 6 did not have spine surgery. After treatments, 8/13 (62%) realized improvement of distressing symptoms selecting very much better, much better or somewhat better on the PGI-I. Four of the patients maintained improvement, reporting minimum PGAD/GPD distressing symptoms at 4-6 months following the last LiSWT. The adverse event of temporary worsening of back pain was observed in 5 patients, noted for 1- 14 days post-treatment, that fully resolved in all patients.

**Conclusion:** While more research is needed, initial results are promising for this non-invasive, non-hormonal, non-pharmacologic shockwave energy-based strategy for a highly selected population of women with distressing PGAD/GPD secondary to suspected radiculopathy of sacral spinal nerve roots.

*CLINICAL RELEVANCE: An Emerging Indication for Shockwave Therapy. There are no major clinical experience reports on this topic in the field yet. SWT could be used for treatment of patients with PGAD/GPD suspected to be from radiculopathy of the sacral spinal nerve roots.*

*DEVICE: MTS urogold100, unfocused applicator OP155.*

Yih et al., 2020:

**Proposed Mechanisms of Erectile Function Improvement with Low Intensity Shock Wave Therapy: Vascular and Erectile Tissue Health Changes Pre- and Post-Treatment**

*San Diego Sexual Medicine.*

21st Annual Fall Scientific Meeting of Sexual Medicine Society of North America (SMSNA), Abstract No.092

**Introduction:** Although Low Intensity Shockwave Therapy (LiSWT) for erectile dysfunction (ED) has been widely used as a non-invasive disease modification strategy, the mechanisms for erectile function (EF) improvement need further elucidation.

**Objective:** The goal was to enhance understanding of proposed vascular mechanisms of EF improvement by objectively examining blood flow and erectile tissue health parameters in ED patients prior to and following LiSWT.

**Methods:** This was a retrospective chart review of men with ED who underwent  $\geq 6$  LiSWT treatments (Urogold 100 MTS) over a 12 month period, underwent baseline and post-treatment grayscale and Doppler ultrasound (GDUS), and completed a patient global impression of improvement (PGI-I) after treatment. Typical LiSWT treatment parameters involved 600 shocks each to dorsal, ventral, right/left lateral penile shaft, right/left crura during erection using the parabolic reflector probe (OP-155), energy flux density 0.13mJ/mm<sup>2</sup>, 3 Hz, membrane pressure 3. A pharmacologic erection with erection hardness score sustained at 3-4 /4 was achieved for the GDUS. B-mode ultrasound (Aixplorer 15.4 MHz transducer) was performed with predetermined settings to avoid reader bias. Four images were captured in the axial plane from the dorsal penile surface at the proximal penile shaft at a fixed dynamic range of 70 dB with three B-mode gain values of increased brightness: 45%, 55% and 65%. Then the dynamic range was lowered to 49 dB and B-mode gain identified (25% - 35%) that provided the best black/white grayscale discrimination. This was repeated at the midshaft and distal penile shaft, yielding 12 cross sectional images/patient. Erectile tissue homogeneity/inhomogeneity of proximal, midshaft and distal cross-sectional areas were determined as follows: normal grayscale had no inhomogeneity (hypo- or hyper-echoic regions); mild inhomogeneity <25%, moderate inhomogeneity 25% - 50%, and severe inhomogeneity >50% hypo- or hyper-echoic regions respectively. De-identified images were read by two experienced readers reaching consensus regarding degree of absent or present hypo- or hyper-echoic regions. Measurements of right/left cavernosal artery peak systolic velocity (PSV) and cavernosal artery right/left end-diastolic velocity (EDV) values were recorded.

**Results:** 31 patients met inclusion criteria. 18/31 (58%) patients had improved erectile tissue homogeneity post-LiSWT from baseline, 4/31 (13%) remained the same and 9/31 (29%) worsened. 12/31 had improved erectile tissue homogeneity in the proximal section, 12/31 in the distal section although not the same 12, and 14/31 in the midshaft. 22/31 patients (71%) rated PGI-I as improved and 11/18 (61%) of patients who expressed improvement on PGI-I had GDUS evidence of erectile tissue improvement. Of those with baseline pre- and post- PSV and EDV measurements, 19/27 (70%) patients had an increase in PSV measurement and 8/27 (30%) had a decrease in EDV measurement. Mean PSV increase was 13.06 cm/s and mean EDV decrease was 2.48 cm/s. 9 patients with EDV of 0 cm/s pretreatment remained unchanged. The figure below shows improved erectile tissue homogeneity in the midshaft comparing baseline severe inhomogeneity to post-treatment mild inhomogeneity.

### Midshaft

7/17/19 Baseline



B Mode Gain 20-35%;  
Dynamic Range 49 dB

B Mode Gain 65%;  
Dynamic Range 70 dB

B Mode Gain 55%;  
Dynamic Range 70 dB

B Mode Gain 45%;  
Dynamic Range 70 dB

10/1/19 Post 6 LiSWT Treatments



B Mode Gain 20-35%;  
Dynamic Range 49 dB

B Mode Gain 65%;  
Dynamic Range 70 dB

B Mode Gain 55%;  
Dynamic Range 70 dB

B Mode Gain 45%;  
Dynamic Range 70 dB

**Conclusion:** This study shows that the mechanisms by which LiSWT for ED improves, in part, erectile function involve enhanced erectile tissue health, increased cavernosal arterial peak systolic velocity and decreased end-diastolic velocity.

*CLINICAL RELEVANCE: Treatment of ED with SWT is a relatively new application area, although it is now well established. This study confirms the underlying mechanisms by which SWT restores erectile function.*

*DEVICE: MTS urogold100, unfocused applicator OP155.*

### Pözl et al., 2020:

#### Exosome Isolation after in vitro Shock Wave Therapy

Department of Cardiac Surgery, Medical University Innsbruck; Institute of Clinical and Functional Anatomy, Innsbruck Medical University.

J Vis Exp. 2020 Sep 10;(163).

Shock wave therapy is routinely applied in orthopedic indications including tendinopathies such as lateral epicondylitis (tennis elbow) and Achilles tendinitis (heel spurs) as well as non-healing wounds and bones. Despite different pathologies, the combination of an angiogenic and an anti-inflammatory effect of shock wave therapy leads to regeneration in soft tissue and bones. In over 30 years of clinical application, no side effects were observed. Furthermore, basic research even revealed regenerative effects on ischemic myocardium. In a previous work we could show that the mechanical stimulus of cultured cells is translated via an exosome release into a biological response. However, the exact mechanism remains to be elucidated. Mechanical coupling is crucial when applying shock wave therapy as even small air bubbles can absorb shock waves. The previously described water bath method is a valid method to guarantee adequate and reproducible shock wave application in vitro. We were able to develop a feasible and replicable protocol to isolate exosomes from cultured cells after shock wave application. Thereby we demonstrate a possibility to study underlying mechanisms of mechanotransduction as well as the regenerative and angiogenic potential of shock wave released exosomes.

*CLINICAL RELEVANCE: This is a methodological paper on how best to analyze the biological responses of cells in culture after SWT.*

*DEVICE: MTS orthogold180C.*

**Fansa et al., 2020:**

**Efficacy of Unfocused Medium-Intensity Extracorporeal Shock Wave Therapy (MI-ESWT) for Plantar Fasciitis**

*Hospital for Special Surgery, New York, NY, Associate Professor of Orthopaedics, Weill Medical College of Cornell University, New York, NY.*

J Foot Ankle Surg. 2020 Sep 3;S1067-2516(20)30335-5.

Extracorporeal shock wave therapy (ESWT) is a promising treatment for plantar fasciitis (PF), however treatment results have varied due to inconsistencies among types of shock waves treatment and devices used. This retrospective chart review includes patients who underwent EWST using the OrthoGold 100™ shock wave device (MTS, Konstanz, Germany) for PF between January, 2013 and September, 2018. There were 108 patients (119 heels) identified, with a mean age of  $51.7 \pm 16.5$  (Range 21-83) years. Patients were treated weekly for 3 weeks, with 2000 impulses per session at an energy flux density (EFD) between 0.10 and 0.17 mJ/mm<sup>2</sup>. Mean follow-up duration was  $11.5 \pm 9.7$  (Range 3-51) months. Mean pre-ESWT pain visual assessment scale (VAS) improved from  $6.7 \pm 1.7$  to  $2.6 \pm 2.7$  ( $p < 0.001$ ). The Foot and Ankle Outcome Score (FAOS) subscales: pain, function of daily living, function of sports and recreational activities and quality of life domains improved from  $53.7 \pm 14.9$  to  $75.7 \pm 16.7$  ( $p < 0.001$ ), from  $38 \pm 15.2$  to  $71.8 \pm 23$  ( $p < 0.001$ ), from  $55.8 \pm 16.4$  to  $71.4 \pm 18$  ( $p < 0.001$ ), from  $42.4 \pm 21.5$  to  $59.4 \pm 20.3$  ( $p < 0.001$ ) and from  $44.9 \pm 16.4$  to  $69 \pm 23.9$  ( $p < 0.001$ ), respectively. Eighty-eight patients (81.5%) were satisfied with the procedure at final follow-up. Treatment of plantar fasciitis with unfocused shock waves was well tolerated and led to significant pain reduction, functional improvement and patient satisfaction.

*DEVICE: MTS orthogold100.*

*CLINICAL RELEVANCE: Retrospective patient analysis over a period of 5 years with very successful treatment results and high patient satisfaction.*

Witness. The Spark of Life.