Pulsed Signal Therapy® (PST™) for the treatment of Musculoskeletal Disorders – Role in Degradation, Repair & Tissue Restoration –

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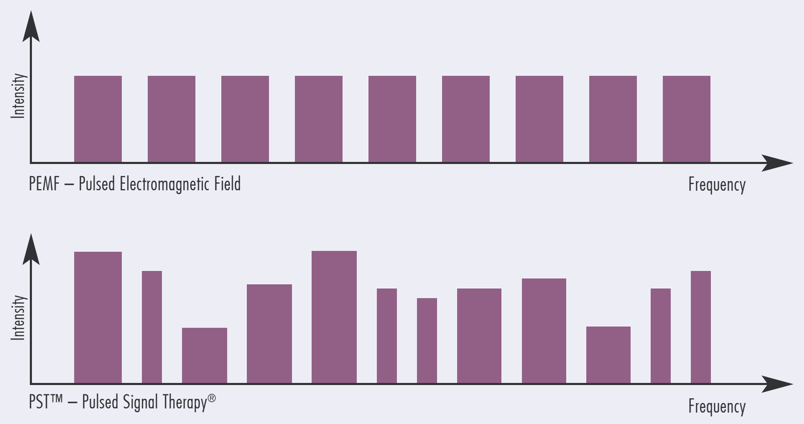
PST Pulsed Signal Therapy Technology

Introduction

Pulsed Signal Therapy® (PST™) is a patented medical technology, developed over 20 years of intense scientific research. It is currently employed in at least 800 clinics and/or medical institutes worldwide. A score of clinical trials and studies have demonstrated PST™ therapeutic success and long-term benefits for the treatment of musculoskeletal conditions, most notably OA. Over ten well-designed *in vitro* studies have confirmed these clinical data. PST™ has been shown not only to be safe and effective, but is painless, non-invasive, non-pharmacological, with long-term follow-up, sustained efficacy and an absence of any known adverse effects.

Unlike conventional therapeutic devices, which deliver alternating current, or at times, direct current at a specific intensity and constant frequency, PST™ delivers changing pulsed electromagnetic signals in an alternating fashion that mimic signals generated in the body.



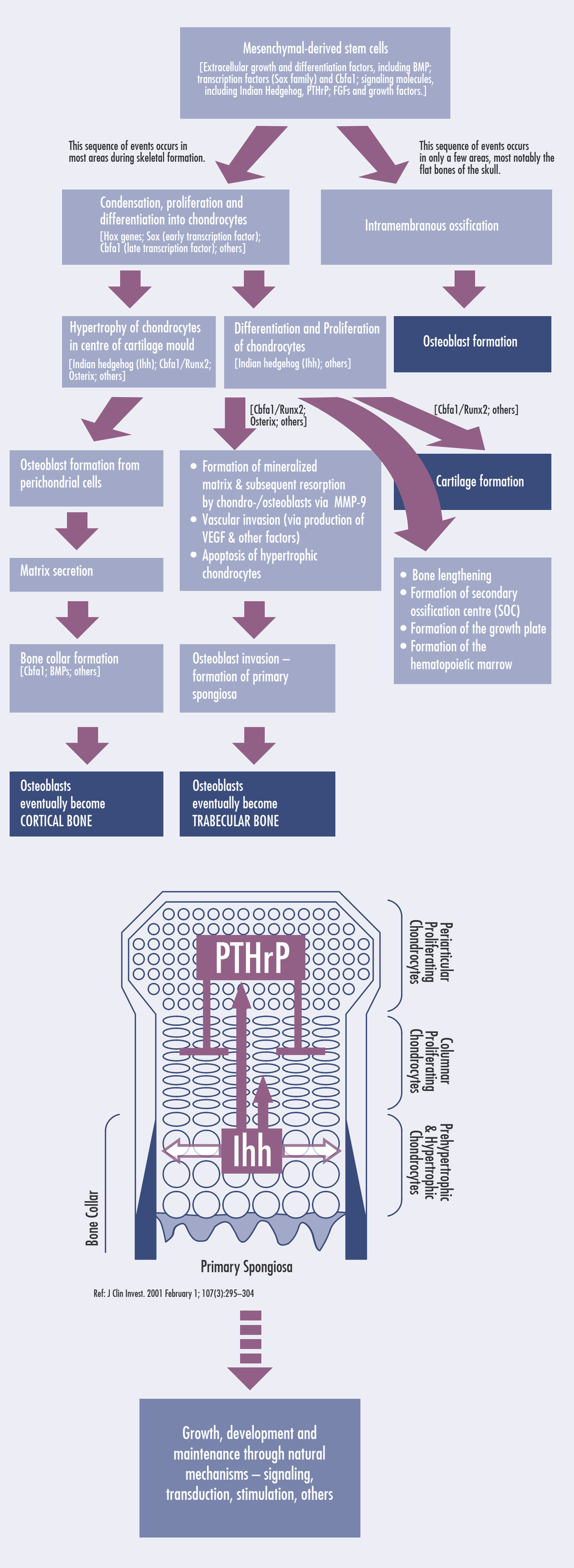
Device Parameter	Magnetic Field Therapy	PST™
Electromagnetic properties	Piezoelectric	Biological signal
Energy form	Alternating current	Direct current
Frequency	44-77Hz	1-30Hz
Waveform	Sinusoidal	Quasi-rectangular
Field strength	2G	12.5G
Energy driver	Voltage control	Pulsed DC
Duty cycle	<50%	>50%
Pulse frequency	Continuous	Pulse-modulated
Frequency source	Fixed frequency source	6 frequency sources
Implementation	Diode (biasing)	Free-wheeling diode

Diverse scientific investigations into PST™ mechanism of action and medical applications for connective tissue disorders continue, with prospective studies underway (refer to table of studies).

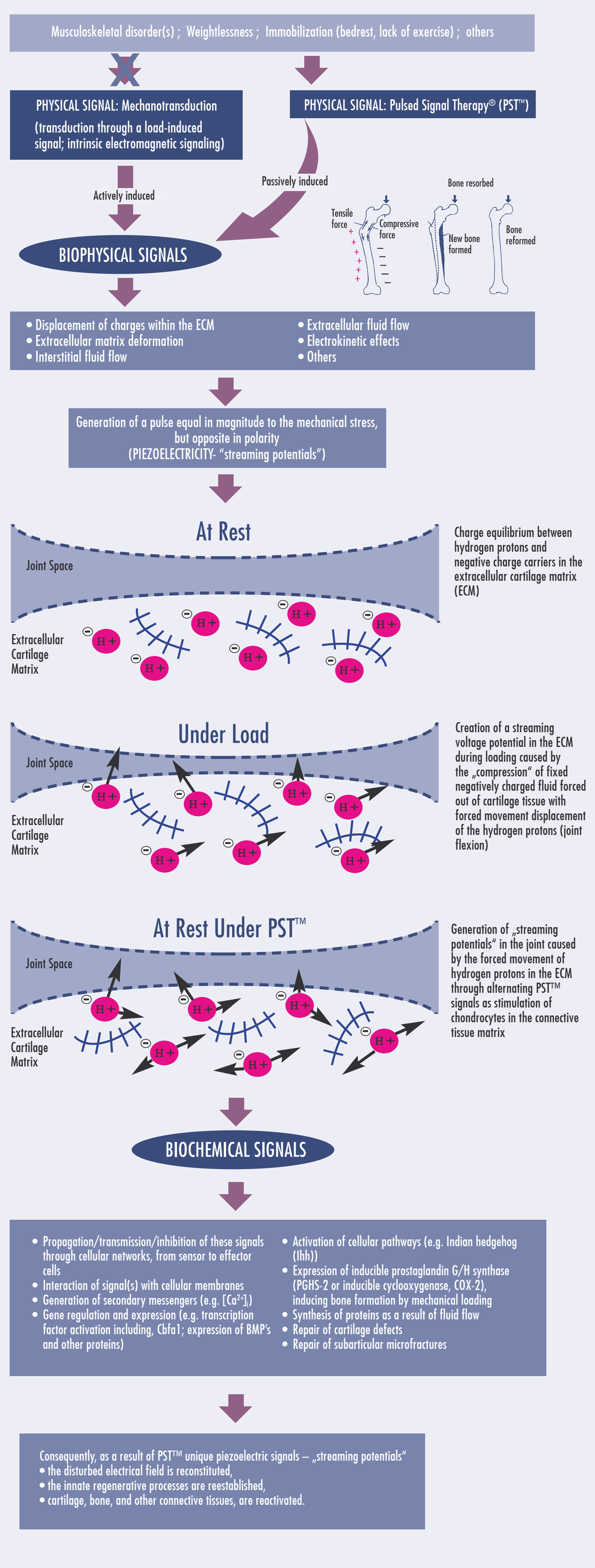
A comprehensive Scientific Information CD containing studies and other relevant information regarding PST™ technology, is available upon request.

Mechanism of Action

A. Normal Developmental Process



B. Pathological Process



Clinical & *in vitro* Studies

Double-blind clinical trials and other open label prospective studies have been conducted and published over a fifteen year period in the USA, Canada, France, Italy, Germany, and Asia, to verify the effectiveness of PST™ proprietary pulsed electromagnetic induction therapy, for the treatment of osteoarthritis and other musculoskeletal disorders of the knee, hip, lower back and cervical spine.

Completed Clinical Studies

DB-1 to DB-4 below are all prospective, randomized double-blind placebo-controlled studies using Extremely Low Frequency Electromagnetic Induction Therapy in the treatment of patients with Inflammatory and Non-Inflammatory Arthritis.

Nature and Duration of Study	Institution where study was conducted & publication(s) (where applicable)	Success rate (%)	Comments
DB-1 & DB-2 (Pilot Studies) A Double-Blind trial of the clinical effects of Pulsed Electromagnetic Fields in Osteoarthritis. 1990 – 1991	Yale University, Connecticut Journal of Rheumatology. 1993; 20(3):456-460.	Approx. 70%	• The difference in means between treated and placebo groups was evaluated by two-tailed t-tests. • Good to very good results, with high statistical significance
DB-3 The effect of Pulsed Electromagnetic Fields in the treatment of Osteoarthritis of the Knee. 1991 – 1992 **DB-4** The effect of Pulsed Electromagnetic Fields in the treatment of Osteoarthritis of the Cervical Spine. 1991 – 1993	Three Trial Centers under a protocol from Yale University, Connecticut Journal of Rheumatology. 1994; 21:1903-1911.	Approx. 70%	• The difference in means between the treated and placebo groups was evaluated by two-tailed t-tests. • Good to very good results, with high statistical significance
Open Initial Trial A Prospective Study Using Extremely Low Frequency Electromagnetic Induction Therapy in the Treatment of Patients with Inflammatory and Non-Inflammatory Arthritis. 1990 – 1991	Yale University, Connecticut.	Approx. 70%	• The difference in means between the treated and placebo groups was evaluated by two-tailed t-tests. • Good to very good results, with high statistical significance
Open Trial 1 A Prospective Study Using Extremely Low Frequency Electromagnetic Induction Therapy in the Treatment of Patients with Inflammatory and Non-Inflammatory Arthritis. 1990 – 1991	Yale University, Connecticut.	Approx. 70%	• Good to very good results, with high statistical significance • PST™ may be effective for treating various joints affected by osteoarthritis, as well as other types of arthritis, and/or other joint-related conditions.
Open Trial 2 A Prospective Study Using Extremely Low Frequency Electromagnetic Induction Therapy in the Treatment of Patients with Inflammatory and Non-Inflammatory Arthritis. 1991 – 1993	Three Trial Centers under a protocol from Yale University, Connecticut.	Approx. 70%	• Good to very good results, with high statistical significance • PST™ may be effective for treating various joints affected by osteoarthritis, as well as other types of arthritis, and/or other joint-related conditions.
Pulsed Signal Therapy: Treatment Of Chronic Pain Due To Traumatic Soft Tissue Injury. 1997 – 1998	McGill University, Vancouver, Canada International Medical Journal. 1999; 6(3):167-173.	72.5%	• Statistically significant improvement in both groups - matched pair t-test analysis of pre- and post-treatment data • PST™ is as effective for the treatment of STI, as it is for OA.
Etude de vérification de l'efficacité antalgique des champs électromagnetiques pulsés (PST™) dans la gonarthrose. [Efficacy of pulsed electromagnetic therapy (PST™) in painful knee osteoarthritis.] (A placebo-controlled double-blind study) 1997 – 1998	Cochin Hospital, Paris, France • American Collegeof Rheumatology Presentation, Nov 1998. • Arthritis Rheum. 1998; 41(3) (suppl): S.357. • arthritis + rheuma. 2002; 22(2):101-104.	76.9% - three months post-treatment	• Statistical significance was obtained after the 9th PST™ treatment and 3 months thereafter - VAS (p<0.01) and Lequesne index (p<0.05). • Good to very good results, with high statistical significance
La PST™ (Terapia a segnale pulsante): proposta di condroprotezione con metodiche fisiche. [PST™ (Pulsed Signal Therapy): A Proposal for a Chondro-Protection with Physical Methods.] (A prospective clinical study of gonarthrosis and non-disc lower back pain.) 1998	Niguarda Hospital, Milano, Italy La Riabilitazione - Revista di Medicina Fisca e Riabilitazione. April-June, 1998; 31(2):51-59.	Knee pain: 17.8% to 68.4% increase in function Lower back pain: 50.5% decrease in pain at 6 weeks post.	• Significant improvement post-treatment • PST™ long-term effects • PST™ is effective in pain management, and in intervening in the pathogenesis of the painful symptoms.
Impiego della Terapia a Segnale Pulsante (PST™) nell'artrosi della mano. [The Use of Pulsed Signal Therapy (PST™) in the treatment of arthritis of the Hand.] 1999 – 2000	Niguarda Hospital, Milano, Italy La Riabilitazione - Revista di Medicina Fisca e Riabilitazione. September, 2000; 33(3):109-114.	76,19% to 80.95% of cases showed success.	• Successful results in 76.19% of cases according to VAS, and in 80.95% according to the algofunctional index. • A significant improvement in a follow-up control, 6 months post-treatment • PST™ long-term effects
Impiego della Terapia a Segnale Pulsante (PST™) nell'artrosi del ginocchio [The Use of Pulsed Signal Therapy (PST™) in Osteoarthritis of the Knee.] 2000 – 2001	Niguarda Hospital, Milano, Italy La Riabilitazione - Revista di Medicina Fisca e Riabilitazione. December, 2001; 34(4):213-218.	71.4% to 87% cases showed success.	• Successful results were obtained in 71,4% of cases according to VAS, and in 87% of cases according to the algofunctional index. • High statistical significance
Procedural proposal for patients suffering with osteoarthritis of the knee by means of PST™ vs. placebo. 1999 – 2002	University of Siena, Siena.	Success in more than 50% of the cases.	• A statistically significant difference was found between both treatment groups.
Risultati preliminary nel trattamento di lesioni osteocondrali di ginocchio trattate con Pulsed Signal Therapy (PST™). [Preliminary results of the treatment) of osteochondral knee injuries, with Pulsed Signal Therapy (PST™).] 2001	Università degli Studi di Catania	50% improvement after the first week of treatment; 100% 3 months post-treatment	• A median value of 2.5, 3 months after treatment, was obtained for subjective pain using VAS. • An overall decrease in pain and improved quality of life • High statistical significance
Risultati a lungo termine della terapia a segnale pulsante (PST™). [Long-term results achieved by Pulsed Signal Therapy (PST™).] 1998 – 1999	Niguarda Hospital, Milano, Italy La Riabilitazione - Revista di Medicina Fisca e Riabilitazione. January-March, 1999; 32(1):11-15.	85.26%, improvement in functionality, one year post-treatment.	• 85.26% was the average obtained, following assessment based on 10 tests of functionality. • PST™ long-term effects decreased pain intensity and improved functionality, 1 year post-treatment
Prospective, clinical verification study of PST™ in Gonarthrosis, Coxarthrosis and degenerative disorders of the lumbar spine. 1997	PST™ Treatment Center Munich, TU Munich • Medycyna Sportowa. December 1998; XIV(89):31-34. • Presentation: Norddeutsche Orthopädenvereinigung e.V. 48.Jahrestagung in Münster, June 1999. • Poster Presentation: 14. GOTS, June 1999, München.	73.9%	• A reduction in the original complaints, with regard to all four investigation parameters, in 73.9%, according to VAS. • High statistical significance
Ergebnisse einer multi-zentrischen Untersuchung zur Wirksamkeit der Pulsierenden Signal Therapie (PST™) Arthrosen im Kniegelenk (Gonarthrose, Stadium II und III nach Kellgren). [Results of a multicenter study of the clinical effect of Pulsed Signal Therapy in Arthrosis of the knee (Gonarthrosis, grade II and III, according to Kellgren.)] 1999 – 2001	Ludwig-Maximilians-Universität, Munich Orthopädische Praxis. 2001; 37(11):701-709.	73% of patients responded positively to PST™.	• Unpaired and paired results for the Lequesne Knee Arthritis Index pre-PST™ and 6 months after PST™, using Mann-Whitney U and Wilcoxon tests (p<0.0001 and p<0.001, respectively) (asymp. 2-tailed) • Both unpaired and paired results for VAS responses, pre-PST™ and 6 months after PST™, showed p<0.0001 (2-tailed). • Both unpaired and paired results for responses to daily activities (DA), pre-PST™ and 6 months after PST™, showed p<0.0001 (2-tailed). • High statistical significance
Permanent Prospective Study (VITAL) 1996 – 2001	Ludwig-Maximilians-Universität, Munich	73% responded positively to PST™.	• The results were based on the Lequesne index and VAS. • High statistical significance
Therapie der anterioren Diskusverlagerung ohne Reposition mit Pulsierender Signal-Therapie (PST™). [Pulsed Signal Therapy in the treatment of anterior disk displacement without reduction.] (An observational study) Ended 1998	Humboldt-Universität, Berlin Deutsche Zahnärztliche Zeitschrift mit Deutsche Zahn-, Mund- und Kieferheilkunde. April 1999; 54(4):284-287.	73%	• SPSS software and Friedman test were used for statistical evaluation of the recorded data (p<0.05). • Post-treatment, 58% of patients could successfully open their jaws to within 37.0 – 40.5 mm. • Significant reduction in pain
Pulsierende Signaltherapie zur Behandlung von Arthropathien des Kiefergelenks – vorläufige Ergebnisse einer Doppelblindstudie. [Pulsed Signal Therapy for the treatment of temporomandibular arthropathy – preliminary results of a double-blind study.] 1997 – 1998	Humboldt Universität, Berlin	Significant success	• Measurements were made using VAS (0-100%). • Significant reduction in pain • Improvement in moving and opening the lower jaw
Morbus Tinnitus (A pilot study) 1999 – 2000	ENT Medical Centre	At 12 weeks 52% were significantly improved and 22% symptom free.	• Definite and significant improvement in 52% of patients (Goebel-Hiller) • PST™ long-term effect
Chronischer Mobus Tinnitus (A pilot study) 1999 – 2001	Medical Centre	• A definite improvement was found 3 months post-treatment. • PST™ long-term effect	
Tinnitus Randomized Multicenter Double-Blind Clinical Study. 1999 – 2002	Clinics and Medical Practices Presentation at the HNO Congress in Dresden, Germany, 27-05-2003.	• A significant decrease in the Tinnitus grade (severity), post the 12-day treatment, at 6 weeks and 3 months thereafter (p>0.05). • PST™ long-term effect	
Three Prospective Clinical Trials conducted in Berlin, Nuremberg and Munich, Germany, on Chronic Tinnitus (Grades, II, III, or IV). 1997 – 2000	Clinics and Medical Practices	• Significant improvement in 52% of the patients • Trend in improvement post-treatment and 6 weeks later, in an additional 25% of patients. • No adverse side effects	

Completed *in vitro* Studies

Nature of Study	Institution where the study was conducted	Publication	Comments
The stimulation of chondrocyte metabolism by pulsed magnetic fields.	North Shore University Hospital, New York (affiliated with Cornell University), USA	• Manuscript, 1992.	• Sulphate incorporation (p<0.05) following PST™ exposure to *in vitro* cartilage explants (in organ culture) • Increase proteoglycan levels - evidence for repair and/or relief in osteoarthritis
Pulsed Signal Therapy (PST™) enhances the proteoglycans concentration in human chondrocyte cultures.	Institute of Rheumatology, University of Siena, Siena, Italy	• Bioelectromagnetics Society [BEMS] Twenty-Second Annual Meeting Abstract Book, Munich, Germany, June 11-16, 2000: 48. • Ann Rheum Dis. 2002; 61:1032-1033.	• Stimulation of IL-b treated chondrocytes with PST™ resulted in restoration of cell structures and proteoglycan synthesis (p<0.05). • No significant differences in cell cultures subjected to pressure cycles • Enhanced cartilage repair, increased [3H]-thymidine incorporation, and [35SO4] uptake (glycosaminoglycan production) observed by transmission electron microscopy (TEM) and scanning electron microscopy (SEM), of PST™-treated cells.
Pulsed Signal Therapy (PST™) Stimulates Mitosis of Human Chondrocytes in Culture.	Praxis für Orthopädie und Sportstraumatologie, Cologne, Germany	• Singapore Humanitas Press, In Proceedings: Tenth International Conference on Biomedical Engineering, Singapore, December 2000; 473-474.	• Statistically significant higher mitosis rates in human chondrocyte cell cultures exposed to PST™.
Der Einfluss der Pulsierenden Signal Therapie auf die Synthese der Extracelluaren Matrix in 3-Dimension Human Chondrozyten. [The PST™ Effect on 3-Dimensional Chondrocyte Culture: An *in vitro* study].	University Center, Charité, Humboldt University, Berlin, Germany	• Presentation at the Deutsches PST™ Symposium [PST™ Symposium], Salzburg, Austria; May 19, 2001. • Presentation at the 1st Biennial Meeting of the Tissue Engineering Society ETES -2001 Symposium of the International Cartilage Repair Society (ICRS) - Freiburg, Germany, Nov. 7-10, 2001.	• Biochemical analysis showed increased deposition of collageneous matrix components, in meniscal and arthritic chondrocyte cultures, treated with PST™. • Articular chondrocyte cultures showed a marginal enhancement of collagen synthesis. • Meniscal chondrocyte cultures showed significant long-term matrix formation (up to 6 months), post-PST™ stimulation.
Study of the clinical effect of PST™ with trials of the synovial liquid in gonarthrosis.	Auguste-Victoria-Hospital Berlin, University of Erlangen	• Conducted 1998 – 2001 • Submitted for publication.	• Statistically significant difference in MMP-1 and 9 levels, between pre- & post-PST™ treatment (2-tailed t-tests) • Increased MMP-1 and 9 levels suggest PST™ may ensure the rapid onset of restoration of damaged tissue – CATABOLISM (p<0.05). • Statistically significant difference in pain intensity, pre- and post-treatment, with a decrease over time – PST™ long-term effect (p<0.05)

Current Clinical Studies

„Study"	Investigators	Location(s)
Ortho Clinical Improvement of Gonarthrosis after Pulsed Signal Therapy® (PST™), is accompanied by an increase in intra-articular Matrix Metalloproteinases and markers of regeneration.	Faensen M, Neise B, Da Silva Ferreira DM, Martin H, Markoll R, Toohil TK and Schuppan D. *In press*	University of Erlangen, Germany
Osteo Long-term, Multicenter Post-Marketing Surveillance Investigations of Pulsed Signal Therapy® (PST™) for the treatment of Osteoporosis.	Dr J. Semler[1], Dr. B. Muche[1], Dr M. Dornacher[2], D. Da Silva Ferreira[3], Dr H. Martin[3], Dr R. Markoll[3]	1) Immanuel-Krankenhaus Rheumaklinik, Berlin-Wannsee 2) ProGelenk Zentrum, Berlin-Wilmersdorf 3) Infinomed - Institute for Innovative Medicine, München 4) Selected medical centers in Germany
Tinnitus	Dr Vitztum	Magdeburg, Germany
Dental	Dr Rotlauf	Munich, Germany

The Effects of PST™ on Synovial Fluid Matrix Parameters, as well as Matrix Metalloproteinases and their Inhibitors, during Joint Remodeling

Background

Clinical (>25) and *in vitro* studies, have consistently verified PST™ as an innovative and successful treatment modality for connective tissue disorders. The following *in vitro* study further confirms the positive effects of PST™ in connective tissue regeneration (evidenced by increased proteoglycan and collagen synthesis), by its important role in favourable joint remodeling, through (controlled) release of Matrix Metalloproteinases (MMPs).

Aim

To investigate whether PST™ plays a significant role in favourable remodeling in Osteoarthritis, by its (controlled) release of Matrix Metalloproteinases (MMPs).

Methodology

Patient Selection

20 patients with gonarthrosis stage II and III (7 women and 13 men; average age 57), complying to specific selection criteria, partook in the study, after signing a formal consent form.

Selection Criteria	Exclusion Criteria
Gonarthrosis stage II and III	History of surgery to the respective joint in the last 6 months
≥30 years of age	Intra-articular injections in the last 3 months
Body mass index ≤32.5	Rheumatic or malignant diseases
No change in medication or physical therapy for at least one month prior to onset of treatment (during the study, no change in medication was allowed)	Inflammation of the soft tissues
Minimum of 10 points on the Lequesne Index	Relevant misalignment or contractures
An understanding of the visual analogue scale for pain intensity	Physical limitation by, or experience of, painful coxarthrosis
Voluntary compliance to partake in the study (signed consent form), after receiving a comprehensive explanation of the study design.	Pregnancy

Aspiration of Synovial Fluid

1.5-2.0ml of synovial fluid was aspirated from the arthrotic knee and kept frozen at -70°C for subsequent analysis (when no fluid could be aspirated, 20ml of physiologic saline was first injected into the joint, the joint carefully maneuvered and thereafter the required 1.5-2.0 ml aspirated). The concentration of each matrix parameter measured was normalized to protein content (measured by the Bradford-method), since protein concentrations in each synovial sample varied. Samples were collected pre-PST™ and at 8 weeks ±2 days post end of treatment.

Treatment

As per protocol, the arthrotic knee was subjected to nine consecutive 1-hour therapy sessions with allowed interruption not exceeding 2 days.

Pain Intensity and Activities of Daily Living

The severity of gonarthrosis, in terms of pain, mobility and daily activities, was assessed according to the Lequesne Index. Using a 10cm/10 point VAS, two days before treatment, patients assessed their pain intensity:

- upon awakening in the morning,
- at night during rest,
- ascending and descending stairs,
- standing for 15 minutes,
- descending stairs alone.

The final exam was at 8 weeks ±2 days post end of treatment.

Determination of Matrix Related Molecules

Matrix Parameter	Method used for Quantification
TIMP-1 tenascin-C collagen type IV collagen type VI MMP-2 MMP-9/TIMP-1 complex	• Monoclonal antibodies in sandwich immunoassays performed in an automated analyzer employing fluoresceine-labelled capture and alkaline phosphatase-labeled detection antibodies. • Immune complexes were separated from serum using magnetic particles covered with monoclonal anti-fluoresceine.
hyaluronan	Biotin-labeled cartilage link protein and alkaline phosphatase-labeled streptavidine.
MMP-1 MMP-3	Commercially available kits (R&D Systems, Wiesbaden, Germany).

All samples were assayed in batches, with appropriate quality controls (calibration with a set of 3 normal sera and 2 pathological joint fluids), and intra- and interassay variation kept below 10%.

Statistical Evaluation

The 2-tailed paired t-test (95% confidence interval) was used to evaluate statistical significant differences between pre- and post-PST™. Ratios of the diverse parameters, pain intensity scores and ADL were assessed.
Pearson correlation (alpha 0.05) was used to determine clinical significance between pre- and post-PST™ differences in pain measures and pre- and post-PST™ differences in ratios of the parameters.

Results

The 2-tailed paired t-tests demonstrated a statistically significant improvement (p<0.05) in all pain intensity scores and ADL activities 8 weeks ±2 days post end of PST™ treatment (Figure 1 and 2).

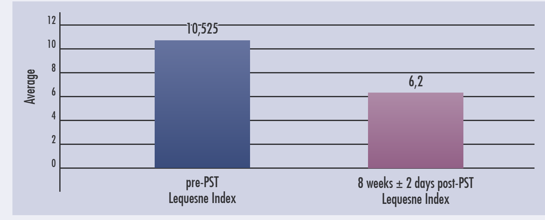


Figure 1: Lequesne index pre- and 8 weeks ±2 days post-PST™ treatment.

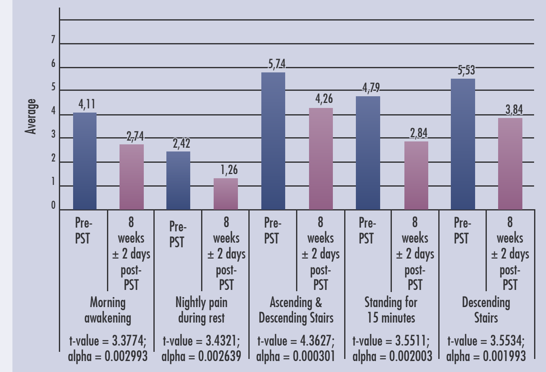


Figure 2: Self assessment of pain and difficulties with activities of daily living (VAS), pre- and 8 weeks ±2 days post-PST™ treatment.

Statistically significant levels of MMP-1/protein, MMP-9/TIMP-1, MMP-9/collagen IV, and tenascin-C/protein were measured post-PST™ treatment (Figure 3). This suggests that PST™ initiates or accelerates the onset of repair processes involving ECM degradation and regeneration. All other measured ECM parameters, or their ratios, measured in synovial fluid, were not significantly different post-PST™ treatment, or showed only an increasing (for example, tenascin-C/protein, hyaluronan/protein, collagen IV), or decreasing (for example, MMP3/TIMP, TIMP1/tenascin-C, collagen IV/hyaluronan) trend.

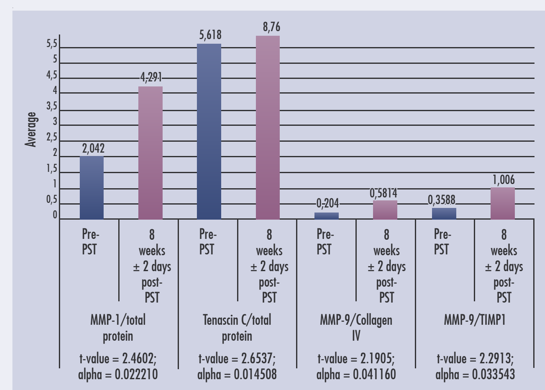


Figure 3: Statistically significant differences in ECM parameter ratios pre- and 8 weeks ±2 days post-PST™ treatment.

Correlation of the clinical results obtained, with measured (changes in) levels of ECM parameters in synovial joint fluid 8 weeks ±2 days post-PST™ treatment, demonstrated that improvement in pain and ADL, as assessed by VAS, correlated with parameters associated with ECM breakdown and repair (Table 1).

		Pearson Correlation	Significance
Morning Awakening	collagenVI/hyaluronan	0.472	0.015
	MMP2/MMP3	0.440	0.023
	MMP2/hyaluronan	-0.419	0.029
During Nightly Rest	MMP9/tenascin-C	0.380	0.045
	TIMP1/hylaluronan	-0.413	0.031
	collagen IV/hyaluronan	-0.429	0.026
	collagen VI/hyaluronan	-0.478	0.014
Ascending and Descending Stairs	MMP3/MMP9	0.451	0.020
	MMP3/collagen VI	0.399	0.036
	MMP3/hyaluronan	0.459	0.018
	collagen IV/collagen VI	0.383	0.043
Descending Stairs	MMP3/MMP9	0.378	0.046
	MMP3/hyaluronan	0.426	0.027
	TIMP1/hyaluronan	0.425	0.027
	collagen IV/hyaluronan	0.387	0.042
	collagen VI/hyaluronan	0.419	0.029

Table 1: Significant correlations between pre- and post*-PST™ differences in pain intensity, and pre- and post*-PST™ differences in ratios of ECM parameters

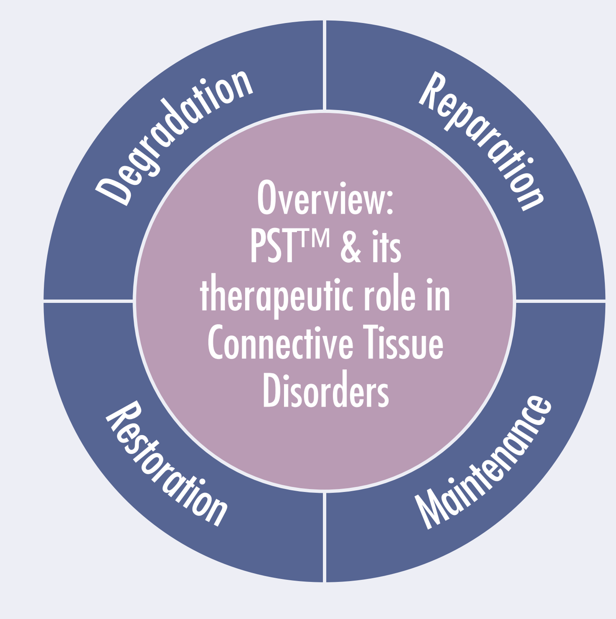
Note 1: A positive correlation indicates that a decrease in pain is accompanied by a decrease in the respective ratio.

Note 2: * = 8 weeks ±2 days post end of treatment

Conclusion

Taken together, we could demonstrate for the first time that the clinical improvement of gonarthrosis by Pulsed Signal Therapy® is accompanied by a moderate increase in, and most likely activation of, intra-articular MMPs and ECM remodeling. In view of the known side effects of MMP-inhibitors, the paradigm of inhibiting matrix metalloproteinases to improve OA (and RA) should be met with a note of caution.

General Medical Applications



PST™ for the treatment of Osteoporosis | 1: Pilot Study

Preliminary Data

Aim

To investigate the effects of Pulsed Signal Therapy® (PST™) on both Trabecular and Cortical Bone Density.

Study Design

Selection Criteria	Exclusion Criteria
1. Postmenopausal women (of at least 3 yrs) 2. Below the age of 75 3. An established Osteopenia, or onset Osteoporosis (no fractures) Trabecular Bone Density: -1,5SD < x < -2.8SD] 4. No change in medication for at least 1 year 5. Voluntary, written compliance to partake in the study, after a comprehensive explanation of the study design. (With the exception of calcium (1000mg/day) and Vitamin D3 (800-1000 units/day), no new medication for osteoporosis was prescribed.)	1. A history of previous fractures 2. Diabetes 3. Morbus Crohn 4. Colitis ulcerosa 5. Hyperthyroidism. 6. Oral corticosteroids (within the last 6mths) 7. New medication prescribed for OP within the last year. 8. Pregnancy 9. Pacemakers

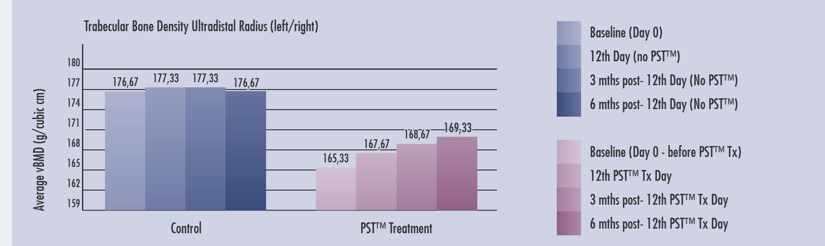
Methodology

The volumetric bone mineral density (vBMD) of both trabecular and cortical bone was measured at the ultradistal radius (wrist), using validated instruments of measurement (VIMs) warranted for wrist density measurements. Each patient served as her own control - that is, one wrist was subjected to PST™ treatment and the other not (the control). Measurements were conducted and recorded for both wrists. During the entire duration of the study, patients were refrained from carrying out any form of physical training, in order to avoid inducing bone formation indirectly through mechanical loading. In this way, any increase in bone formation observed, could be attributed to PST™.

Treatment protocol:
A one-hour daily treatment with PST™, for 12 days, with no treatment over the weekend. Follow-ups conducted at 3-months, 6-months and 12-months, post-PST™ treatment.

Results

These are preliminary results based on a randomized sampling from a population group of post-menopausal women fitting the mentioned selection criteria.
Since trabecular bone turnover rate is greater than cortical bone turnover rate, it was expected that the greatest change in vBMD measurements, would be observed when assessing trabecular bone. As early as 12 days post PST™-treatment, an increase in trabecular vBMD was observed.



Graph 1: Results of Patients Treated with PST™ compared to controls

Graph 1 depicts the results of both the control (that is, the wrist NOT subjected to PST™ treatment), and the wrist treated with PST™. In the control group, no significant changes in vBMD were observed. However, at the end of treatment, an increase in trabecular vBMD was observed in the wrist subjected to PST™, which continued increasing at 3- and 6-months post end of treatment. This increasing trend suggests a balancing (restoration) of the resorption and formation processes, characteristic of bone remodeling, by PST™.

Conclusion

This study suggests that PST™ has positive effects on bone formation and that it functions to restore the innate balance of remodeling. In the long-term, it is postulated that PST™ will continue to stimulate bone formation, and retard bone resorption, until the innate balance between bone formation and bone resorption has been restored.

PST™ for the treatment of Osteoporosis | 2: current investigation

Long-term, Multicenter Post-Marketing Surveillance Investigations of Pulsed Signal Therapy® (PST™) for the treatment of Osteoporosis.

Study Design

Postmenopausal Women, under the age of 75
BMD measurements: DEXA (DXA)

- Group 1: Osteoporosis (OP) with BMD: x < -2,5SD
  No Fractures
  Medication allowed: Vitamin D and Calcium only
- Group 2: as for 1, but on bisphosphonates + Vitamin D & Calcium
  No change in OP medication over the past year
- Group 3: as for 2, with a history of a previous vertebral fracture
  No change in current OP medication
- Group 4: All patients not classified under Group 1, 2, or 3
  OP/Osteopenia, x< -1,5SD

Selection Criteria

- Postmenopausal women (at least in their 2nd year), over the age of 50, with an established osteopenia/osteoporosis
- Below the age of 75
- No indication of secondary osteopathies
- Voluntary, written compliance to partake in the study, after a comprehensive explanation of the study design

Exclusion Criteria

- Cancer treatment within the last year
- Pacemaker
- Hyperthyroidism
- Morbus Crohn
- Colitis ulcerosa
- Hypercalcaemia
- Indications of other/secondary osteopathies
- (serious venosity)
- Long-term use of corticosteroids (excluding corticosteroid inhalation/topical)
  - doses of at least 7,5mg Prednisolone equivalents/day over a period of at least 6 months
  - doses of less than 7,5mg Prednisolone equivalents/day (long-term therapy greater than 1 year)
- 6 months after discontinuing with hormone replacement therapy
- Group 1: a case history of any (or earlier) osteoporosis therapy (with the exception of calcium and Vitamin D

Methodology - Overview

- Pre-treatment: Patient signed consent form, case history
- Treatment: 12, 1-hour treatment sessions
- Follow-up evaluations: 6 weeks, 3-, 6-, and 12-months
- Measurements:
  - DEXA (DXA): vertebral and hip (colum femoris) measurements, pre-PST™ and at follow-ups
  - Laboratory: assessment of PST™ effects using bone formation and resorption markers, including alkaline phosphatase and beta-crosslaps in serum, pre-PST™ and at follow-ups. NTX in urine, calcium, BSG, gamma-GT and creatinine will also be measured.
  - VAS and Neuromuscular tests (pre-PST™ and at follow-ups)
  - Morphometry (Group 3 only): pre-PST™ and 12-months post-PST™

Discussion

Pulsed Signal Therapy® therapeutic success in Musculoskeletal Disorders, most notably in osteoarthritis, has been well established, presented at well-respected international conferences and published in numerous international, scientific and medical journals – an integrative CD is available upon request. Prospective *in vitro* and *in vivo* studies are planned to continue investigations into PST™ multifaceted medical application in the treatment of diverse connective tissue disorders, through its positive inductive effects on various innate, interconnected, network/signaling pathways.

Biophysically, it has been established that PST™ emulates the innate physiological and mechanical stresses evoked and required in bone and cartilage formation. It passively induces fluid flow and ionic displacement, thereby generating a piezoelectric effect ("streaming potential"). These biophysical signals in turn, activate various signaling network paths – as in mechanotransduction. Increased proteoglycan levels, and collagen synthesis, have been observed *in vitro*, following stimulation with PST™ (Fioravanti *et al* 2002, Krüger *et al* 2001).
One of PST™ inductive effects and subsequent (signal) pathway activation was observed in a clinical study involving patients with Gonarthrosis Stage II and III, where increased intra-articular MMPs and markers of regeneration were measured, 8 weeks ±2 days post-PST™ treatment (study in press). In particular, levels of MMP-1/protein, MMP-9/TIMP-1, MMP-9/collagen IV, and tenascin-C/protein were statistically and significantly increased, 8 weeks ±2 days post-PST™ treatment. MMP-9 is of particular importance in angiogenesis and endochondral ossification during bone development (Takahara *et al* 2004, Kim *et al* 2000, Maes *et al* 2002). Another MMP important in connective tissue development is MT1-MMP. MT1-MMP deficient mice have been shown to develop osteopenia, arthritis and fibrosis of the soft tissues (Vu *et al* 2000). In addition, they lacked vascular canal formation that generally results in delayed ossification until vessels invaded the zone of hypertrophic cartilage through the perichondrium. This delay resulted in decreased chondrocyte proliferation, leading to progressive fibrosis. The positive effects of PST™ in bone remodeling has been shown in preliminary data from a pilot study on postmenopausal women, with osteoporosis, treated with PST™. It could therefore be postulated that the increase in bone formation observed, may be attributed, in part, to PST™ positive effects on MMPs and markers of regeneration, namely MMP-9.

Indeed, biomolecular investigations into PST™ (bio)potential may extend this treatment paradigm beyond the borders of the musculoskeletal system…

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