A non-drug, non-invasive treatment for osteoarthritis of the knee
Arthritis: The "Coming Epidemic"

- 45 million people in U.S. with some form of arthritis
- 21 million people with osteoarthritis (OA)
- 10 million OA knee
  - 6 million symptomatic despite best drug therapy ($26 billion)
  - 400,000 total knee replacements/year ($1.4 billion)

Time Magazine, Dec. 9th, 2002
## Current Treatments for OA of the Knee

<table>
<thead>
<tr>
<th>Non-Selective NSAID’s</th>
<th>Cox II’s</th>
<th>OAdjuster</th>
<th>BIO-1000</th>
<th>Hyalurons</th>
<th>Arthroscopy</th>
<th>Total Knee Replacement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pill</td>
<td>Pill</td>
<td>Brace</td>
<td>EStim</td>
<td>Injection</td>
<td>Surgery</td>
<td>Surgery</td>
</tr>
</tbody>
</table>

- **NSAID’s**: Non-Selective NSAID’s, Cox II’s
- **BIO-1000**: Pill
- **Hyalurons**: Injection
- **Arthroscopy**: Surgery
Electrical Stimulation for the Treatment of Osteoarthritis of the Knee

- Non-drug, non-invasive treatment
- Targeted pain relief
- Delivers mild electrical stimulation to knee
- Proven in published clinical studies
FDA Clearance for Osteoarthritis of the Knee

BioniCare® BIO-1000™ System cleared by the FDA for U.S. marketing

- Unique indication
  “For use as an adjunctive therapy in reducing the level of pain and symptoms associated with osteoarthritis of the knee and for overall improvement of the knee as assessed by the physicians global evaluation (see clinical studies).”

- Safety
  Only transient, mild skin rash
BioniCare Patient: Female, 50

2 Years Ago  1 Year Ago  After 9 Months of Treatment
BioniCare Patient: Female, 50
Sequential X-rays of Knee

Baseline

Year 1

Year 2
Osteoarthritis Overview
Definition of Osteoarthritis

- Osteoarthritis (OA) is primarily a noninflammatory degenerative disorder of movable joints characterized by an imbalance between the synthesis and degradation of the articular cartilage, leading to the classic pathologic changes and destruction of cartilage.
## OA of the Knee Risk Factors

<table>
<thead>
<tr>
<th>EXTRINSIC</th>
<th>INTRINSIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Congenital Anomalies</td>
</tr>
<tr>
<td>Weight</td>
<td>Bone density</td>
</tr>
<tr>
<td>Genetics</td>
<td>Alignment</td>
</tr>
<tr>
<td>Occupational overuse</td>
<td>Quadriceps strength</td>
</tr>
<tr>
<td>Inactivity</td>
<td>Ligament Laxity</td>
</tr>
<tr>
<td></td>
<td>Proprioception</td>
</tr>
</tbody>
</table>
## OA General Features

<table>
<thead>
<tr>
<th>Clinical</th>
<th>Laboratory</th>
<th>Radiographic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;50</td>
<td>ESR &lt;40 mm/hour</td>
<td>Osteophytes</td>
</tr>
<tr>
<td>Morning stiffness &lt;30 minute</td>
<td>RF Titer &lt;1:40</td>
<td>Joint space narrowing</td>
</tr>
<tr>
<td>Crepitus</td>
<td>Non-inflammatory synovial fluid</td>
<td>Subchondral cysts and sclerosis</td>
</tr>
<tr>
<td>No inflammation</td>
<td></td>
<td>Malalignment</td>
</tr>
<tr>
<td>Bony enlargement or tenderness</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Joint affected by osteoarthritis

- Bone
- Muscle
- Tendon
- Capsule (reinforced by ligaments) is thickened
- Cartilage becomes rough and thinner
- Synovial fluid
- Synovial membrane (synovium) is thickened and inflamed
- Osteophyte
Osteoarthritis

Healthy knee joint

Hypertrophy and spurring of bone and erosion of cartilage
OA Osteophytes
OA Medial Compartment Narrowing
# OA Treatments Face a Changing Environment

<table>
<thead>
<tr>
<th>Non-Selective NSAID’s</th>
<th>Cox II’s</th>
<th>OAdjuster</th>
<th>BIO-1000</th>
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<td>EStim</td>
<td>Injection</td>
<td>Surgery</td>
<td>Surgery</td>
</tr>
</tbody>
</table>

![Images of treatments](image1.png)

- **Restrictions**
- **N.N.D.**
Osteoarthritis Therapy NSAIDs

- Block prostaglandin production to relieve pain and inflammation

- Examples
  - Cox I inhibitors: Indocin, Feldene, Naprosyn, Voltaren, Butazolidin, Motrin, Dolobid, Aleve,
  - Cox II inhibitors: Celebrex, Vioxx, Bextra
NSAI Ds

- Advantages
  - Rapid onset
  - Cox I - relatively cheap
  - Good (NOT GREAT) analgesics
  - Adequate therapy for most OA patients
NSAI Ds

- Disadvantages
  - Cox I: Ulcers, GI bleeding, platelet abnormalities, renal toxicity
  - Cox II: Expensive, increased edema, CHF in susceptible individuals
OA Surgery

- Types
  - Osteotomy
  - Hemiarthroplasty
  - Arthroplasty
  - Arthrodesis
  - Arthroscopy
  - Arthrocentesis
  - Carticel
OA Osteotomy
OA Hemiarthroplasty
OA Total Knee Arthroplasty
OA Total Knee Arthroplasty

Shaved head of tibia

Prosthesis in place
## Outcomes After Total Joint Replacement
(The Dartmouth Atlas of Musculoskeletal Health Care)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Primary TJR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of Stay</td>
<td>5.33 days</td>
</tr>
<tr>
<td>Prolonged hospitalization (more than 10 days)</td>
<td>5.3%</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>0.97%</td>
</tr>
<tr>
<td>Discharge to skilled nursing facility</td>
<td>33.3%</td>
</tr>
<tr>
<td>Re-hospitalization within 3 months</td>
<td>15.8%</td>
</tr>
<tr>
<td>Revision within 2 years</td>
<td>2.7%</td>
</tr>
<tr>
<td>Another primary replacement within 2 years</td>
<td>8.0%</td>
</tr>
<tr>
<td>Dislocations at 1 year</td>
<td>2.3%</td>
</tr>
</tbody>
</table>
Use of Electrical Stimulation
History of Electrical Stimulation of Bone/Cartilage

- 1812: First attempt to heal non-union with electrical shock
- 1953: Osteogenesis at cathode in rabbit femur
- 1957: Piezoelectric effect of bone discovered
- 1960-70: Electrical healing of fractures in animals and in vitro osteoblast stimulation experiments
- 1971: First human non-union fracture healing
History of Electrical Stimulation of Cartilage

- 1972  Bassett showed mechanical stimuli generate electrical fields in cartilage
- 1974  Lotke – electromechanical properties of human cartilage demonstrated
- 1978  Rodan – electrical fields increase DNA synthesis in chondrocyte
- 1988  Okihana – Electrical fields DNA and proteoglycan synthesis in cartilage
- 1980  Electrical biology of cartilage examined in over 90
- 2004  Peer reviewed publications
Evidence in Support of Direct Effects of Electric Fields on Chondrocytes

- 1978: Rodan GA – Science
- 1978: Bassett – Metabolic Surgery
- 1982: Nogami H – Clinical Orthopedics and Related Research
- 1985: Binderman – Biochemical and Biophysical Acta
Evidence in Support of Direct Effects of Electric Fields on Chondrocytes

- 1991: Sakai – International Orthopedics
- 1994: Caldwell – Arthritis and Rheumatism
- 1996: Liu – Osteoarthritis and Cartilage
- 2003: Ciombor – Osteoarthritis and Cartilage
- 2004: Wang – Clinical Orthopedics and Related Research
BIO-1000 System
Specifications
BIO-1000 System Patient Use at Home
## Differentiation of Products and Technology

### Indications for Use

<table>
<thead>
<tr>
<th>BioniCare® BIO-1000™ System</th>
<th>Osteogenesis Stimulator</th>
<th>TENS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjunctive therapy in reducing the level of pain and symptoms associated with osteoarthritis of the knee, and for overall improvement of the knee as assessed by the physician’s global evaluation.</td>
<td>Treatment of nonunion and delayed union fractures and congenital pseudoarthroses of the bone</td>
<td>Adjunctive treatment of post-surgical and post-traumatic acute pain, and symptomatic relief and management of acute and chronic intractable pain</td>
</tr>
</tbody>
</table>
## Differentiation of Products and Technology

<table>
<thead>
<tr>
<th></th>
<th>BioniCare® BIO-1000™ System</th>
<th>Osteogenesis Stimulator</th>
<th>TENS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target Tissue</strong></td>
<td>Cartilage</td>
<td>Bone</td>
<td>Nerve</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>Clinically Proven</td>
<td>Clinically Proven</td>
<td>Data controversial</td>
</tr>
<tr>
<td><strong>Signal</strong></td>
<td>Negatively-spiked Direct Current</td>
<td>Direct Current or Alternating Current</td>
<td>Alternating Current</td>
</tr>
<tr>
<td><strong>Analgesia Onset</strong></td>
<td>Within 1 Week</td>
<td>None</td>
<td>Within .5 hour</td>
</tr>
<tr>
<td><strong>Analgesia Offset</strong></td>
<td>Months - Years</td>
<td>N/A</td>
<td>Within .5 hour</td>
</tr>
<tr>
<td><strong>Placebo controlled, double blind, sub-threshold trials</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Animal Study</strong></td>
<td>Cartilage Regeneration</td>
<td>Bone Healing</td>
<td>No</td>
</tr>
</tbody>
</table>
The BIO-1000 System
Pulsed Electrical Stimulation Waveform

Output Waveform: signal is negatively-spiked, asymmetrical DC output
## BIO-1000 System Electrical Specifications

<table>
<thead>
<tr>
<th>Specification</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency</strong></td>
<td>100 +/- 5 Hz, fixed, digital</td>
</tr>
<tr>
<td><strong>Waveform</strong></td>
<td>Monophasic spike-shaped pulse, analog generated</td>
</tr>
<tr>
<td><strong>Voltage Output Range</strong></td>
<td>0-12 volts - Channel 1 or 2, digital</td>
</tr>
<tr>
<td><strong>Voltage Pulse Width</strong></td>
<td>1.8ms @ 10% pt. of peak</td>
</tr>
<tr>
<td></td>
<td>0.64ms @ 50% pt. of peak</td>
</tr>
<tr>
<td><strong>Current Output Range</strong></td>
<td>0-24mA peak @ 500 ohms resistive load</td>
</tr>
<tr>
<td></td>
<td>0.2mA average @ 500 ohms resistive load</td>
</tr>
<tr>
<td><strong>Current Pulse Width</strong></td>
<td>1.8ms @ 10% pt. of peak @ 500 ohms resistive load</td>
</tr>
<tr>
<td></td>
<td>0.64ms @ 50% pt. of peak @ 500 ohms resistive load</td>
</tr>
<tr>
<td><strong>Display</strong></td>
<td>LCD</td>
</tr>
<tr>
<td><strong>Power Source</strong></td>
<td>9 volt battery</td>
</tr>
</tbody>
</table>
Proposed Mechanism of Action
Normal Cartilage
Healthy Cartilage
Endogenous Electrical Fields

Unloaded

Loaded by mechanical pressure

Fluid velocity

Unloaded
Degeneration of Cartilage with Osteoarthritis

Degenerative process accelerated

Cartilage deterioration aggravated

Homeostasis impaired
Pulsed Electrical Stimulation (PES) to restore cartilage homeostasis

1. Cartilage with OA
2. PES restores electrical fields in cartilage
3. Homeostasis restored
Conclusions

- Endogenous electric fields are an essential biophysical stimulus to cartilage homeostasis.
- This stimulus is compromised in the progression of Osteoarthritis due to the loss of aggrecan and decreased mechanical properties.
- The BioniCare® BIO-1000™ System replaces the endogenous field with an exogenous field of comparable magnitude.
Conclusions (continued)

- Daily use of this System provides the necessary stimulus to enable chondrocytes to achieve the putative cartilage repair observed in both published animal studies and in controlled human studies submitted to the FDA.
BioniCare Clinical Resources
Scientific Advisory Board

- Roland W. Moskowitz, M.D., Co-Chairman
  - Case Western Reserve University
  - Northeast Ohio Multipurpose Arthritis Center
- J. Timothy Harrington, M.D., Co-Chairman
  - University of Wisconsin
- Carl T. Brighton, M.D., Ph.D.
  - University of Pennsylvania
- David S. Hungerford, M.D.
  - The Johns Hopkins School of Medicine
  - Good Samaritan Hospital, Baltimore
Scientific Advisory Board

- Jacques R. Caldwell, M.D.
  - BioniCare Medical Technologies
- Daniel E. Furst, M.D.
  - Division of Rheumatology, UCLA
- Jean Pierre Pelletier, M.D.
  - Université de Montréal
- Solomon R. Pollack, Ph.D.
  - University of Pennsylvania
Clinical Studies

- Zizic, et. al.

- Mont/Hungerford Abstract

- Lippiello, et. al.
Zizic, et. al. Osteoarthritis of the Knee Study
BioniCare Osteoarthritis of the Knee Study

- **Design**
  - Placebo controlled
  - Randomized
  - Double blind

- **Multi-center**
  - Five sites
  - Seventy-eight patients

- **Treatment**
  - Eight ± two hours daily (home)
  - Four weeks

- **Journal of Rheumatology 1995**
Study Patients Encompassed a Classic OA Profile

<table>
<thead>
<tr>
<th></th>
<th>Active</th>
<th>Inactive</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong> (yr), p=0.15</td>
<td>62</td>
<td>66</td>
</tr>
<tr>
<td><strong>Height</strong> (m), p=0.89</td>
<td>1.72</td>
<td>1.73</td>
</tr>
<tr>
<td><strong>Weight</strong> (kg), p=0.49</td>
<td>92</td>
<td>88</td>
</tr>
<tr>
<td><strong>Female</strong>, p=0.62</td>
<td>49%</td>
<td>43%</td>
</tr>
</tbody>
</table>
The Kellgren Scale

The Kellgren scale was developed by J. Kellgren and J. Lawrence in 1952 and is a radiological assessment tool used to determine the degree of severity of osteoarthritis in a patient.

The scale uses five radiological features to demonstrate evidence of osteoarthritis:

- The formation of osteophytes on the joint margins
- Periarticular ossicles
- Narrowing of joint cartilage associated with sclerosis of subchondral bone
- Small pseudocystic areas in the subchondral bone
- Altered shape of the bone ends, particularly in the femur
Kellgren Scale con’t

- The scale is divided into five grades
  - None    (0)
  - Doubtful (1)
  - Minimal (2)
  - Moderate (3)
  - Severe  (4)
Baselines: Patients Were Significantly Symptomatic Despite Optimal Therapy

Primary Outcome Measures

<table>
<thead>
<tr>
<th></th>
<th>Active (N=41)</th>
<th>Inactive (N=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global (p=0.74)</td>
<td>5.68</td>
<td>5.55</td>
</tr>
<tr>
<td>Pain (p=0.70)</td>
<td>6.21</td>
<td>6.03</td>
</tr>
<tr>
<td>Function (p=0.84)</td>
<td>6.07</td>
<td>6.35</td>
</tr>
</tbody>
</table>
Optimal Therapy Was Maintained Throughout the Study: Concomitant Medication

<table>
<thead>
<tr>
<th>Patients</th>
<th>NSAIDs (p=0.29)</th>
<th>Analgesics (p=0.20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active (N=41)</td>
<td>Inactive (N=37)</td>
</tr>
</tbody>
</table>

- **NSAIDs**: 80% Active, 60% Inactive
- **Analgesics**: 40% Active, 20% Inactive

$p$-values: 0.29 (NSAIDs), 0.20 (Analgesics)
Physician Global Evaluation
Intent to Treat (N=78)

Active (N=41) vs Inactive (N=37)

Improvement

Baseline | Week 1 | Week 2 | Week 3 | Week 4
---|---|---|---|---
1.1 | 1.3 | 1.8 | 2.3 | 2.1

p=0.023
Physician Global Evaluation
Time Compliant Completers (N=53)

Active (N=32)  Inactive (N=21)

Baseline 0.0 0.0
Week 1 0.9 0.6
Week 2 1.4 1.1
Week 3 2.0 1.0
Week 4 2.3 2.3

p<0.001
Patient Evaluation of Pain and Symptoms
Intent to Treat (N=78)

Baseline Week 1 Week 2 Week 3 Week 4

Improvement

Active (N=41)  Inactive (N=37)

p=0.033

Patient Evaluation of Pain and Symptoms
Intent to Treat (N=78)
Patient Evaluation of Pain and Symptoms
Time Compliant Completers (N=53)

Improvement

Baseline  Week 1  Week 2  Week 3  Week 4

Active (N=32)  Inactive (N=21)

Baseline: 0.0  0.9  1.1  0.8  1.0
Week 1: 1.3  1.5  1.9
Week 2: 1.5  1.9
Week 3: 1.9
Week 4: 2.2

p<0.013
Patient Evaluation of Function
Intent to Treat (N=78)

Improvement

Baseline Week 1 Week 2 Week 3 Week 4
Active (N=41) Inactive (N=37)

p=0.178
Patient Evaluation of Function
Time Compliant Completers (N=53)

Baseline Week 1 Week 2 Week 3 Week 4

Improvement

Active (N=32) Inactive (N=21)

p<0.029
Osteoarthritis of Knee
Patients with $\geq 50\%$ Improvement - Intent to Treat

Number of Primary Efficacy Outcomes

- Active
- Inactive

p$<0.05$
Osteoarthritis of Knee
Morning Stiffness - Intent to Treat

Patients

Improvement by ≥ 15 minutes

47%

25%

p<0.05

Active
Inactive
Osteoarthritis of Knee
Range of Motion - Intent to Treat

Improvement by > 5 degrees flexion

<table>
<thead>
<tr>
<th>% Patients</th>
<th>Active</th>
<th>Inactive</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>45%</td>
<td>18%</td>
</tr>
<tr>
<td>20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

p<0.05
Outcomes Summary from Zizic, et. al.

- No serious or systemic adverse events
- Physicians Global Evaluation:
  - Time compliant responders exhibited 130% more improvement than placebo responders
- Patient Evaluation of Pain and Symptoms
  - Time compliant responders exhibited 120% more improvement than placebo responders
- Patient Evaluation of Function
  - Time compliant responders exhibited 33% more improvement than placebo responders
- 50% Responders
  - 24% of patients on active device exhibited a >50% improvement on all 3 primary endpoints versus 6% for placebo
- Significant improvement in morning stiffness and range of motion (Goniometer)
Mont/Hungerford TKA Deferral Study
Mont/Hungerford TKA Deferral Study

- Design
  - Historical matched controls (Johns Hopkins)
  - Open treatment
  - 4-Year Study
  - Patients had one TKA

- Multi-Center
  - 23 sites
  - 157 TKA candidates
  - 101 controls

- Treatment
  - 8 + 2 hours daily (home)
  - Mean 11 months (range 3 to 51 months)

- Presented at AAOS 2004
Baseline Disease Severity

Primary Clinical Outcome Measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>No Surgery (N=95)</th>
<th>Surgery (N=62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global</td>
<td>7.1</td>
<td>7.2</td>
</tr>
<tr>
<td>Pain</td>
<td>6.7</td>
<td>7.0</td>
</tr>
<tr>
<td>Function</td>
<td>6.5</td>
<td>6.7</td>
</tr>
</tbody>
</table>

BioniCare® distributed by RSMedical

(p=0.78) Pain (p=0.34) Function (p=0.65)
### BioniCare/Johns Hopkins TKA Deferral Study (All Patients)

<table>
<thead>
<tr>
<th>Year</th>
<th>TKA Deferral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BioniCare® (157)</td>
</tr>
<tr>
<td>1</td>
<td>83%</td>
</tr>
<tr>
<td>2</td>
<td>75%</td>
</tr>
<tr>
<td>3</td>
<td>65%</td>
</tr>
<tr>
<td>4</td>
<td>60%</td>
</tr>
</tbody>
</table>

\[ P < 0.0001 \]
Total Knee Deferral
Severe at Baseline
BioniCare=103, Control=42

Total Knee Arthroplasty Deferral Patients

- **BioniCare**
- **Control**

p<0.0001

Year

0 1 2 3 4
Outcomes Summary from Mont/Hungerford

- No serious or systemic adverse events
- Despite increased disease pathology, the BIO-1000 Continued to maintain efficacy across all endpoints
  - Physicians global evaluation
  - Patient evaluation of pain and symptoms
  - Patient evaluation of function
- Deferral of total knee arthroplasty
  - For all patients, at the end of 4 years 60% of BIO-1000 patients deferred TKA versus 35% of patients in the matched control
  - For the most severe patients, 62% of BIO-1000 patients deferred TKA versus 7% of patients in matched control
BioniCare Patient: Female, 50

- 2 Years Ago
- 1 Year Ago
- After 9 Months of Treatment
BioniCare Patient: Female, 50
Sequential X-rays of Knee

Baseline
Year 1
Year 2
Lippiello, et. al. Cartilage Repair Study
BioniCare Cartilage Repair Study on Rabbit Treatment Protocol

- Groups 1 and 2
  - 1.2mm: 4 hours/day, 5 days/week for 2 weeks (total of 40 hours), sacrifice at 8 and 26 weeks

- Group 3
  - 3.2mm: 4 hours/day, 5 days/week for 2 weeks (total of 40 hours), sacrifice at 8 weeks

- The Journal of Orthopaedic Research 1990
BioniCare Cartilage Repair Study on Rabbit (Lippiello, et al)  A – Control  B – Active

FIG. 1. (A) Photomicrograph of 1.2 mm osteochondral defect stained with Safranin O. Repair in unstimulated animal sacrificed at 8 weeks. Short arrows indicate the right margin of the wound, long arrows mark the extrusion-like appearance of fibrous tissue forming a pannus over articular cartilage. (B) Similar section taken from animal stimulated for 40 h. Arrows indicate margin of defect. Note the extensive remodelling activity in subchondral bone beneath the defect site as well as the presence of cartilage islands stained with Safranin O (C).
Outcomes Summary
Lippiello, et al

- Hyaline Articular Cartilage Growth with BIO-1000 Signal
  - First non-invasive production of Hyaline Cartilage
  - Multiple defect models
  - After 2 weeks of treatment rabbits developed Hyaline Articular Cartilage
  - Present at 2 months
  - Stable at six months

- First In-Vivo Measurement of Electrical Fields in Articular Cartilage
Presenter’s additional slide(s)