Bioactive Wound Dressing
Contents

Company Profile: Biopharm / Freudenberg

Bioactive Wound Dressing: GDF-5 & Scaffold

- Technical Feasibility
- Pre-clinical Investigation

Key Facts
Biopharm GmbH

Biotechnology Company
- Founded 1986 in Heidelberg, privately owned
- Two business divisions, 35 highly skilled employees
- 2100m² laboratory and office space in Heidelberg and in Eppelheim
- GLP / GMP-certified

Business activities
- 2 major license deals with Johnson & Johnson and SCIL/Medtronic
- Three drug candidates in clinical trials
- Intellectual Property: 25 patent families with 160 issued patents
- Member of the Association of Research-Based Pharmaceutical Companies (vfa)
## Biopharm GmbH: Project Status

<table>
<thead>
<tr>
<th>Orthopaedic indication</th>
<th>Patent protection</th>
<th>In-vitro / In-vivo Proof of concept</th>
<th>Toxicology preclinical development</th>
<th>Clinical development</th>
<th>Market authorisation</th>
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</thead>
<tbody>
<tr>
<td>Degener. Disc Disease (J&amp;J)</td>
<td>(RenuDisc Clin. Phase I / II) <strong>GDF-5</strong></td>
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<tr>
<td>Maxillofacial (Scil/Medtronic)</td>
<td>(MD05-I Ready for Clin. Phase III) <strong>GDF-5</strong></td>
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<tr>
<td>Maxillo-facial surgery</td>
<td>(MD05-P Ready for Clin. Phase III) <strong>GDF-5</strong></td>
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<td>Regenerative products for dentistry</td>
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<tr>
<td>Bone regeneration</td>
<td><strong>BB-1</strong></td>
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<tr>
<td>Fracture Healing / Osteoporosis</td>
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<td>Osteoarthritis</td>
<td><strong>New Mutant</strong></td>
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<td>Wound healing</td>
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<tr>
<td>Tissue regeneration</td>
<td><strong>GDF-5/Scafolene</strong></td>
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<tr>
<td>(Skin wounds)</td>
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</table>

## Neurology

| CNS Parkinson’s disease PNS Peripheral nerve regeneration | **GDF-5** | | | | |
| | | | | | |

*GDF-5*
The Freudenberg Group

- Family company
- Over 160 years old
- 16 Business Groups
- 37,000 Employees
- Operating in 58 countries
- 6,007 billion EUR in 2011
# The Freudenberg Group

## Freudenberg & Co. Kommanditgesellschaft

### Freudenberg SE

**Seals and Vibration Control Technology Business Area**
- Freudenberg Sealing Technologies
- NOK-Freudenberg Group China
- Freudenberg Oil & Gas
- Freudenberg Schwab Vibration Control
- EagleBurgmann
- Dichtomatik
- Helix Medical
- Trelleborg/Vibracoustic

**Nonwovens and Filtration Business Area**
- Freudenberg Nonwovens
- Freudenberg Filtration Technologies
- Freudenberg Politex Nonwovens

**Household Products Business Area**
- Freudenberg Household Products

**Specialties and Others Business Area**
- Freudenberg Chemical Specialities
- Freudenberg NOK Mechatronics
- Freudenberg IT
- Freudenberg New Technologies
  - Division
  - Freudenberg Real Estate Management
  - Freudenberg Service Support
  - Freudenberg Insurance Service
# Freudenberg New Technologies

## New Businesses
- New Business Development
- **scaffolene**
- Fuel Cell Components Technology
- Venture Capital
- Strategic R&D

## R & D Services (FFD)
- Physics and Simulation
- Material and Failure Analysis
- Polymers and Processing
- Chemistry and Surface Technology
- Patents, Trademarks, Information
- Senior Scientists
The Freundenberg Group: Freudenberg New Technologies

Freudenberg New Technologies SE & Co. KG (FNT), will strengthen Freundenberg’s overall innovation performance to the benefit of our customers and for long term financial success. Our culture rewards creativity and initiative by all our employees.

Objective of the New Businesses department is the identification and development of new markets and business opportunities on the basis of Freundenberg technologies and know-how / expertise.

scaffolene by Freudenberg allows our partners to develop real innovations in surgery, active wound treatment and regenerative medicine with short development time lines.
## Contents

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### Key Facts
Bioactive Wound Dressing: Our Motivation

Expanding clinical needs of people with acute and chronic full-thickness defects

Increasing demand for dermal skin replacement and regeneration products

Most products do not achieve desired clinical results

Bioactive wound dressing: Dermal tissue matrix with growth factor
Bioactive Wound Dressing: GDF-5

Triple effect of GDF-5 in Wound Healing

**Skin Repair**

**Angiogenesis**

**Nerve Regeneration**

**Effect of GDF-5**

In-vivo and in-vitro studies show significant effects of GDF-5 on the regeneration of blood vessels, nerves and skin tissue.

**Indication Wound Healing**

GDF-5 addresses critical factors that support effective diabetic foot treatment.

**Mode of action is known (signaling)**
Bioactive Wound Dressing: GDF-5

GDF-5: Recombinant human growth and differentiation factor 5
- Human protein, originally isolated from skin
- 119 amino acid
- Monomer 12.5 kDa
- Dimer 25 kDa
- Expression in E. coli

Achievements
- 20 patent families
- 160 issued patents
- 60 scientific publications
- 2 major license deals

Schreuder et al., BBRC 329: 1076-1086 (2005)
Bioactive Wound Dressing: Scaffold

How does scaffolene differ from existing technologies?
- Unique technology due to the gentle processing of raw materials and biopolymers
- Processing at low temperature, without harmful solvents and polymeric degradation

What is the advantage of scaffolene?
- Enables to convert highly sensitive or atypical polymers into bioresorbable 3D scaffolds
- Allows to incorporate other sensitive bioactive materials (e.g. growth factors etc.) into the bioresorbable nonwoven
What are the key facts of our technology?

- **Platform technology:** More than 80% of all medical approved bioresorbable polymers can be utilized
- **Product variety:** Customized solutions since product features can be adapted to desired specification
- **Manufacturing:** Almost all of the nonwoven standard production technologies can be applied
- **Industrial scale production:** Reliable process, computer controlled, no cross contamination

... and relevant quality standards: The production is in accordance with all the relevant quality standards as ISO 13485
Bioactive Wound Dressing: GDF-5 & Scaffold

Advantages of each technology in wound healing

**Growth factor GDF-5 (Biopharm)**
- Proof of efficacy (animal model), low dose application
- Positive safety data derived from clinical trials
- Tissue regeneration very close to healthy tissue
- Isolated from human skin, highly specific
- Mode of action well known for growth factor GDF-5

**Bioresorbable scaffold (FNT)**
- ECM 3D-matrix polymers enhancing wound healing
- Wound filling by bioresorbable nonwoven
- Local release of growth factor GDF-5
- Bioresorbable, no irritation to the regenerating tissue by change of dressing
- Easy to adapt to rough or irregular surfaces

Synergetic effects will lead to a breakthrough innovation in the field of bioactive wound dressing
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Technical Feasibility: Milestones

Selection of matrix polymers
- Suitable raw materials for wound healing identified (ECM)
- Processing of different polymers (medical grade), alone or in combination with each other

Production of customized scaffolds
- Production of bioresorbable nonwovens
- Initial biocompatibility testing (MCHT1/26 cell line)
- Evaluation of interaction (absorption, release) between scaffold and GDF-5

Incorporation of GDF-5 into fibers
- GDF-5 incorporated into fibers of nonwovens
- Initial trials for preparation of GDF-5 (storage at -80 °C)
- Gentle processing (active feeding) on laboratory scale
Technical Feasibility: Milestones

Recovery of GDF-5 (ELISA)
- GDF-5 incorporated into fibers of nonwovens
- Processing (active feeding) on laboratory scale
- Testing of release and recovery of GDF-5

Biological activity of GDF-5 (ALP assay)
- GDF-5 incorporated into fibers of nonwovens
- Processing (active feeding) on laboratory scale
- Evaluation of GDF-5 release and biological activity by alkaline phosphatase assay (ALP)

Storage capacity of sterilized product
- Upscaling to industrialized production site
- γ-sterilization of final product combination
- Evaluation of GDF-5 recovery (ELISA) and biological activity (ALP) of final product
Technical Feasibility: Conclusion

Achievements

- Industrial scale production of drug-device combination
- Validated processes, reliable results
- Recovery and biological activity of GDF-5 after processing and sterilization (> 70%)
- Proven storage capacity and shelf-life (> 6 months)

What we can offer:

- On-time delivery
- Quality assurance and control
- Adherence to pharmaceutical regulations
- Fully (technically) developed product
- Patented technology
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Pre-clinical Investigation: Clinical Partner

University of Tübingen
- Center of Excellence for Plastic, Reconstructive, Hand and Burn Surgery, BG-Trauma Center, Germany
- Annually approximately 10,000 inpatients and around 26,000 outpatients, about 11,000 surgical procedures
- One of the most prestigious addresses in Germany in the area of trauma and reconstructive surgery, including the care of severe burn

Ethical motivation
- Accelerate dermal wound regeneration
- Avoid painful change of dressings and wound irritation
- Overcome limitations and disadvantages of skin transplantation

Goal
- Clinical support for efficient dermal replacement product, suitable for patients and physician’s needs
Pre-clinical Investigation: Study Design

Animal full thickness model
Goettinger Minipigs
Randomized prospective study

Treatment with novel gelatin / collagen based wound dressing

Healing of deep dermal skin wounds
Planimetric and histologic evaluation

GDF-5

gelatin / collagen scaffold
Pre-clinical Investigation: Study Design

Animal study groups:
- A: Single dose group
- B: Multiple dose group

A: Treatment single dose:
- Amount of animals: 6
- Scaffold-Growth-Factor wound dressing (5 x 5 cm) will be applied topically on Day 1 covering the wounds.

B: Treatment multiple dose:
- Amount of animals: 6
- Scaffold-Growth-Factor wound dressing (5 x 5 cm) will be applied topically covering the wounds on Day 1, 3, 5, 7, 9, 11, 13, 15 and 19.

Type of wounds: Circular wound with a diameter of 20 mm and a depth of 6 mm
- Amount of wounds/animal: 8
- Control groups: One wound remain untreated; three wounds will be covered with the scaffold w/o growth factor.
- Duration: Explantation and histological evaluation after day 21. All animals will be sacrificed after 21 days.
- Evaluation: Histologic and planimetric evaluation, continuously checks of blood serum level of growth factor
Pre-clinical Investigation: Methodology & Evaluation

- Preoperative preparation:
  - Animal conditioning
  - Shaving and tattooing

- Surgical procedure
  - Incision
  - Application and wound treatment

- Postoperative wound management
  - Regular exchange of wound dressing
  - Documentation
# Pre-clinical Investigation: Methodology & Evaluation

<table>
<thead>
<tr>
<th>Methodology/Evaluation</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELISA blood testing</td>
<td>No systemic effect of GDF-5</td>
</tr>
<tr>
<td>Macroscopic</td>
<td>Planimetric evaluation</td>
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<td></td>
<td>Time of wound closure</td>
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<tr>
<td>Necropsy</td>
<td></td>
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<tr>
<td>Microscopic</td>
<td>Histological evaluation</td>
</tr>
<tr>
<td>Epidermal thickness</td>
<td>Healthy skin</td>
</tr>
<tr>
<td>Epidermal thickness</td>
<td>Treated skin</td>
</tr>
<tr>
<td>Epidermal cell number</td>
<td>Treated skin</td>
</tr>
</tbody>
</table>
Pre-clinical Investigation: Time To Wound Closure

- Treatment supports and accelerates wound closure
- Multiple dose application reduces closure time compared to single application
- Scaffold + GDF-5 and Scaffold show comparable results for time to wound closure
Pre-clinical Investigation: Quality Of Wound Closure

Results for epidermal thickness:
- Treatment shows increased epidermal thickness
- Multiple dose application supports epidermal thickness compared to single dose
- Scaffold + GDF-5 optimizes significantly epidermal thickness compared to Scaffold
Pre-clinical Investigation: Quality Of Wound Closure

Results for epidermal cell count:
- Treatment shows increased epidermal cell count
- Multiple dose application optimizes epidermal cell count compared to single dose
- Scaffold + GDF-5 supports significantly epidermal cell count compared to Scaffold
## Pre-clinical Investigation: Summary

<table>
<thead>
<tr>
<th>Day 14</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Untreated control wound</strong></td>
<td><img src="image1.png" alt="Histology" /></td>
</tr>
<tr>
<td><strong>Scaffold (150 g/m²)</strong></td>
<td><img src="image2.png" alt="Histology" /></td>
</tr>
<tr>
<td><strong>Scaffold + GDF-5 (150 g/m² + 500 ng)</strong></td>
<td><img src="image3.png" alt="Histology" /></td>
</tr>
</tbody>
</table>

- Mean wound closure after 13.5 days
- Epidermal layer is thin and not homogenous
- Formation of a granulation tissue appears poorly
- Significantly faster wound closure after 11.0 days
- Neo-epithelium is thicker and smoother, organized in well defined layers
- Complete dermal closure, no signs of inflammation
- Significantly improved quality of wound closure (epidermal thickness and epidermal cell count)
- Well organized granulation tissue
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## Key Facts
Key Facts

Cooperation model
- Create partnership as licenser (Biopharm) and contract manufacturer (FNT)
- Offering an exclusive right in innovative regenerative GDF-5 wound matrix

Our expectation
- Pharmaceutical partner for clinical approval and commercialization
- With leading market position and strong sales organization worldwide
Key Facts

Partner benefit

- Significantly reduced development risk:
  - Efficacy shown in animal experiments
  - Established large scale manufacturing under ISO conditions
  - Human clinical trials can be started within short time frame
  - Patented product
- Innovative and proprietary product concept with unique selling proposition
  (in-vitro: primary cell culture, in vivo: mini pigs)
- Bioactive wound dressing addresses high unmet medical need for dermal tissue repair
- High sales potential in a worldwide growing multi-billion market
Thank you for your attention