Orthopaedic Implant Design from Concept to Commercialization

Engineering + Human Behavior at the Frontiers of Orthopaedic Trauma Research

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Bioscience in the 21st Century
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Overview

Part 1: Tibial Fracture Basics
- Surgical fixation
- Intramedullary (IM) nailing
- Surgical procedure

Part 2: Case Study: OrthoXel Apex IM Nailing System
- Design concept
- R&D process (transition from academia to startup company)
- Commercialization

Part 3: Frontiers in Trauma Research
- Intersection of epidemiology, engineering, clinical care, and human behavior

Part 1: Tibial Fracture Basics

Warning: This section contains some graphic images.
Tibial Fracture

Warning: Unedited images are graphic.

Left: Tennessee Titans’ WR Marc Mariani (2012)
Right: Louisville Cardinals’ Kevin Ware (2013)
Boston Celtics’ Gordon Hayward (2017)
Surgical Fracture Fixation

Intramedullary Nails and Screws

Locking Plate and Screw Systems

Ilizarov Frames and Ring Fixators with Kuntscher Wires

External Fixators with Transcutaneous Pins

Plus many more hybrids and systems designed for small-extremities and specific anatomical challenges.
Secondary Fracture Healing

Secondary Healing
- Formation of an external “callus”
- Evolving mixture of cartilage, fibrous tissue, and new (woven) bone
- Provides temporary structural stability
- Remodels over time

*Medullary Canal*
*Old Cortical Bone*
*Newly Formed Callus*
IM Nailing Surgical Procedure

Patient Recumbent with Flexed Knee

Open Medullary Canal

IM Nailing Surgical Procedure

Insert Guide Wire and Progressively Ream to Get “Chatter”

Select Nail and Attach Insertion Handle

IM Nailing Surgical Procedure

Slide Nail into Medullary Canal

Attach Aiming Arm

IM Nailing Surgical Procedure

Freehand Distal Locking

Guided Proximal Locking

IM Nailing Procedure

Remove Insertion Handle and Insert End Cap

Final Screw Configuration Options

Part 2: OrthoXel Apex IM Nailing System

Medical Device R&D from Concept to Commercialization
Pre-Spinout Development Timeline

Early Concept Name: Flexible Axial Stimulation (FAST) IM Nail

- **2010**
  - Proof-of-Concept Funding Awarded (Enterprise Ireland)
  - Grant Awarded for Ovine Study
  - PCT Filed

- **2011**
  - Cadaveric Study of Micromotion-Enabled IM Nail

- **2012**
  - Pilot Cadaver Study Results Published [6]

- **2013**
  - US/EU Patent Applications
  - Angle-Stable FAST Nail Cadaver Results Published [7]

- **2014**
  - Preclinical Study with MSRU/University Zurich

- **2015**

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Product Design Specification

Intramedullary Nailing of Tibial Fractures

What products already exist?

What should we be trying to do?

What are the constraints?

Critical Analysis of Current Product Offerings and Market Landscape

Comprehensive Review of Fracture Healing Literature

Manufacturability
Clinical Acceptance
Regulatory Pathway
Intellectual Property
Marketability
Market Landscape

The standard of care for fixation of midshaft tibial (shinbone) fractures is intramedullary nailing.

In 2013, the U.S. tibial IM nail market\(^8\):

- $146M market value (ASP $2,350)
- Delivered 62K units (20% of all IM nail procedures)
- Was growth-oriented (4.1% CAGR 2012-2022)
- Had a high three-firm concentration ratio:
  85% (Stryker, DePuy Synthes, Smith & Nephew)

[9] tinyurl.com/SoccerBrokenLeg
Tibial IM Nail Product Offerings

- Stryker T2™ IM Nailing System
- Smith & Nephew TRIGEN™ META-NAIL™
- DePuy Synthes Expert Tibial Nail with Angular-Stable Locking System (ASLS)
- DePuy Biomet VersaNail® Tibial Nailing System
- Zimmer Biomet Natural Nail AND VersaNail
- Orthofix Centro/Tibial Nailing System

2012

2015
Secondary Fracture Healing

1) Inflammation
   - Medullary Canal
   - Cortex
   - Periosteum
   - Hematoma

2) Soft Callus
   - Periosteal Bridging
   - Cartilage

3) Callus Hardening
   - Intramembranous Ossification
   - Endochondral Ossification

4) Remodeling
   - Bone Union: Woven Bone Replaced with Lamellar Bone
   - Callus Resorption

Mechanical Environment at Fracture Site

Speed and Course of Secondary Healing
Importance of Shear Stability

- Sheep received transverse osteotomies of tibia with a 3 mm interfragmentary gap\(^{[11]}\)
- Comparison of standard unreamed IM nailing to an angle-stable configuration with threaded screw holes to prevent torsional shear

Angle-stable locking produced:
- Higher postmortem callus torsional stiffness
- Greater mineralised bone area (black)
- Complete bridging of osteotomy gap (arrows)

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Products with Torsional Stability Focus

Smith & Nephew
TRIGEN™
META-NAIL™
Threaded screw holes and polyethylene bushings reduce angular instability.

DePuy Synthes®
Angular-Stable Locking System (ASLS)
Expert Tibial Nail with expandable bio-resorbable sleeves for “enhanced fixation”.

Biomet®
Phoenix™
Nail System
Internal setscrew locks the proximal oblique screws and 5.0mm of fracture compression.

Zimmer®
Natural Nail™
System
StabiliZe technology links nail and screws to control rotation.

These systems produce highly-rigid constructs.
Is more rigidity better?
Optimizing Construct Stiffness

6 Different Fixators

- Angle-stable nail better than standard nail
- ASTN not as good as fixator with lower stiffness

Stiffness Map and Healing Results

Micromotion Animal Studies

Osteotomized sheep were treated with controlled axial micromotion via an ex-fix. Post-mortem bending stiffness showed that:

- Large gaps delay healing
- For well-reduced fractures (gaps ≤ 3 mm), micromotion distances of:
  - 0.2, 0.5, and 1 mm increase callus stiffness compared to rigid fixation[12-14]

Micromotion Clinical Trials

For a wide range of fracture types, micromotion:

- Stimulates development of proliferative callus
- Significantly reduces healing time

<table>
<thead>
<tr>
<th></th>
<th>Micromotion</th>
<th>vs.</th>
<th>Rigid Fixation</th>
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<tbody>
<tr>
<td>Clinical Union* [16]</td>
<td>13.4 weeks</td>
<td>(N = 38)</td>
<td>18.1 weeks</td>
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<td></td>
<td>(p=0.004)</td>
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<tr>
<td>Independent Weight-Bearing [15]</td>
<td>17.9 weeks</td>
<td>(N = 29)</td>
<td>22.3 weeks</td>
</tr>
<tr>
<td></td>
<td>(p=0.0005)</td>
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Micromotion reduced healing time by approximately 4.5 weeks

* Bending stiffness of 15Nm/deg

The aim of the Flexible Axial Stimulation (FAST) Intramedullary Nail is to produce controlled axial interfragmentary micromotion while maintaining high torsional stability to produce the optimum mechanical environment for accelerated fracture healing.
Product Design Specification

Critical Analysis of Current Product Offerings and Market Landscape

Comprehensive Review of Long Bone Fracture Healing Literature

Manufacturability
Clinical Acceptance
Regulatory Pathway
Intellectual Property
Marketability

Complex and Multifaceted Design Specification

Can we find a simple and elegant solution to satisfy the complex design requirements and achieve maximum clinical benefit?
## Design Constraints/Considerations

| Design for Manufacturability          | • Reduce number of components  
|                                      | • Minimize incremental cost  
|                                      | • Employ standard machining techniques |
| Clinical Acceptance                  | • No added time or complexity in operating theatre  
|                                      | • Accommodate a guide wire  
|                                      | • Backward-compatible with fully-static fixation  
|                                      | • Minimize risk bone on-growth (internal features only) |
| Regulatory Pathway                   | • Accepted materials (no biocompatibility issues)  
|                                      | • Risk analysis/dFMEA/uFMEA (consider device and user failures)  
|                                      | • Line of sight to FDA 510(k) substantial equivalence claim |
| Intellectual Property Protection     | • Broad IP footprint  
|                                      | • Inventive step and non-obviousness  
|                                      | • Provisional, PCT, and country-specific filings |
| Marketability                        | • Unique selling points (device)  
|                                      | • Cost pressures (US vs. EU) |
FAST Nail Concept

Micromotion and torsional stability derived from a proximal stem insert

Insert slides telescopically inside proximal cannulus and ensures axial micromotion

Short slot controls micromotion

Machined features prevent rotation and ensure proximal torsional stability
Design Objective

Generating axial micromotion at the fracture site requires relative movement between proximal and distal locking screws.

How much force is required to induce movement?

Mechanical Testing

- Proximal/distal extremities embedded in PMMA
- Measured forces required to induce micromotion

Micromotion Plateau Force Data

Box plots show median, range, and upper/lower quartiles (N=7 samples)

Weight of hanging shank and foot:

\[ F_{\text{Foot}} = 0.06 \times BW \]
\[ = 4.5 \text{ kgf} \]

Weight of the hanging foot alone is sufficient to cause micromotion without requiring full weight-bearing.

Axial tension/compression, torsion, shear, and four-point bending tests were carried out on implanted prototypes with enhanced torsional stability features.

Measurements were repeated for explanted prototypes mounted in composite tubes (Sawbones).

Preclinical Study

Funding
- Grant from Irish Health Research Board for a large-animal study

Veterinary Research Partner
- Musculoskeletal Research Unit (MSRU) at University of Zurich

Results
- Continuation to commercialization stage was viable
# Translation to Startup Company

<table>
<thead>
<tr>
<th>Before</th>
<th>After</th>
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<tbody>
<tr>
<td>![CIT logo](Cork Institute of Technology) ![CUH logo](Cork University Hospital) ![UCC logo](University College Cork) FAST Tibial Nail</td>
<td><img src="Orthoxel" alt="Orthoxel logo" /> Apex Nailing System (Product Family)</td>
</tr>
<tr>
<td><strong>Objectives:</strong> Research Publications Visibility</td>
<td><strong>Objectives:</strong> Capitalization Regulatory Clearances Product Launch</td>
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</table>
Timeline to Product Launch

Proven Concept Idea

2014

Rebranding

2015

Enhanced Web Presence

2016

CE Mark certification: Initiate distribution of approved product, start post-market clinical evaluation

2017

Fundraising and Company Growth (Hiring)

OEM Supplier Selection and Quality Management Activities

DFM (Implants and Instruments)

IP Management

Regulatory Submissions

2018+

Femoral Nailing System

Images courtesy: www.orthoxel.net
Part 3: Frontiers in Orthopaedic Trauma Research

Innovation at the Intersection of Epidemiology, Engineering, Clinical Care, and Human Behavior
Challenges in Fracture Care

Most of the time...
• Right implant + experienced surgeon + active weight bearing = good healing

But sometimes things go wrong...
• Fracture nonunion
• Who and why?
• Clues from epidemiological models

Other Challenges
• Opioid abuse
• Obesity
• Human behavior
Nonunion Epidemiology

Tibial Fractures

- Injuries most common in young men and often result from risk-taking behaviors (motorcycles, sports)\(^{[17]}\)

Nonunion

- Fracture does not unite after primary surgery and requires additional intervention to stimulate healing (exchange nailing, bone grafting)
- Complex, multifactorial problem
- New data: nonunion is more frequent in middle adulthood, particularly among women, but why?

Nonunion Risk Theory #1

- Nonunion risk may depend on fracture pattern
Nonunion Risk Theory #1 Model Test

- Nonunion risk is driven in part by fracture pattern (AO/OTA Classification)

**42-A Simple Fractures**
- A1 Spiral
- A2 Oblique
- A3 Transverse

**42-B Wedge Fractures**
- B1 Spiral Wedge
- B2 Bending Wedge
- B3 Fragmented Wedge

**42-C Complex Fractures**
- C1 Spiral
- C2 Segmental
- C3 Irregular

Use computational simulations to compare the healing process using simple rules for mechanical stimulation.
Fracture Healing Simulations

Mechanoregulation model: mechanical strain-based rules govern tissue differentiation in the healing zone.

- Distortional (Shear) Strain, $\varepsilon_{Dist}$
- Hydrostatic (Volumetric) Strain, $\varepsilon_{Hydro}$

Simulation methods: ANSYS + MATLAB with Fuzzy Logic Toolbox, loading conditions based on partial weight bearing on IM nail.
Fracture Healing Simulations

Key Results:

- Fracture pattern has a *mechanical* influence on healing
- Models with floating bone fragments (B3, C3) healed most slowly
Required Elements for Healing

Nonunion Risk Theory #2

- Nonunion risk may depend on patient behavior

BIOLOGY
- Metabolic Factors
- Vascularity
- Mechanoregulation

SURGERY
- Choice of Implant
- Accuracy of Reduction
- Soft Tissue Injury Management

STIMULUS
- ???
- = PATIENT
  - Pain (Tolerance and Management)
  - Weight Bearing (Body Mass and Assertiveness)
  - Compliance

Nonunion risk may depend on patient behavior.
Future Study Design:

- Observational studies designed to measure behavior (weight bearing) and quantify the healing response

red = callus region at 12 weeks post-op
The largest callus isn’t always the strongest. Structure and mechanical properties both matter and x-rays can’t provide this information.
Future Directions in Clinical Research

Observational Hypothesis Testing
- More early weight bearing is associated with faster healing
- Higher levels of reported pain are associated with less weight bearing and slower healing

Future Interventional Trials
- Use behavioral interventions to help patients achieve optimal early activity levels, especially in the critical early weeks when pain levels are highest
- Use personal data tracking to help manage pain and activity levels
Sources of Funding

Health Research Board

Collaborators and Support

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Dr. John Galbraith, MRCSI
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