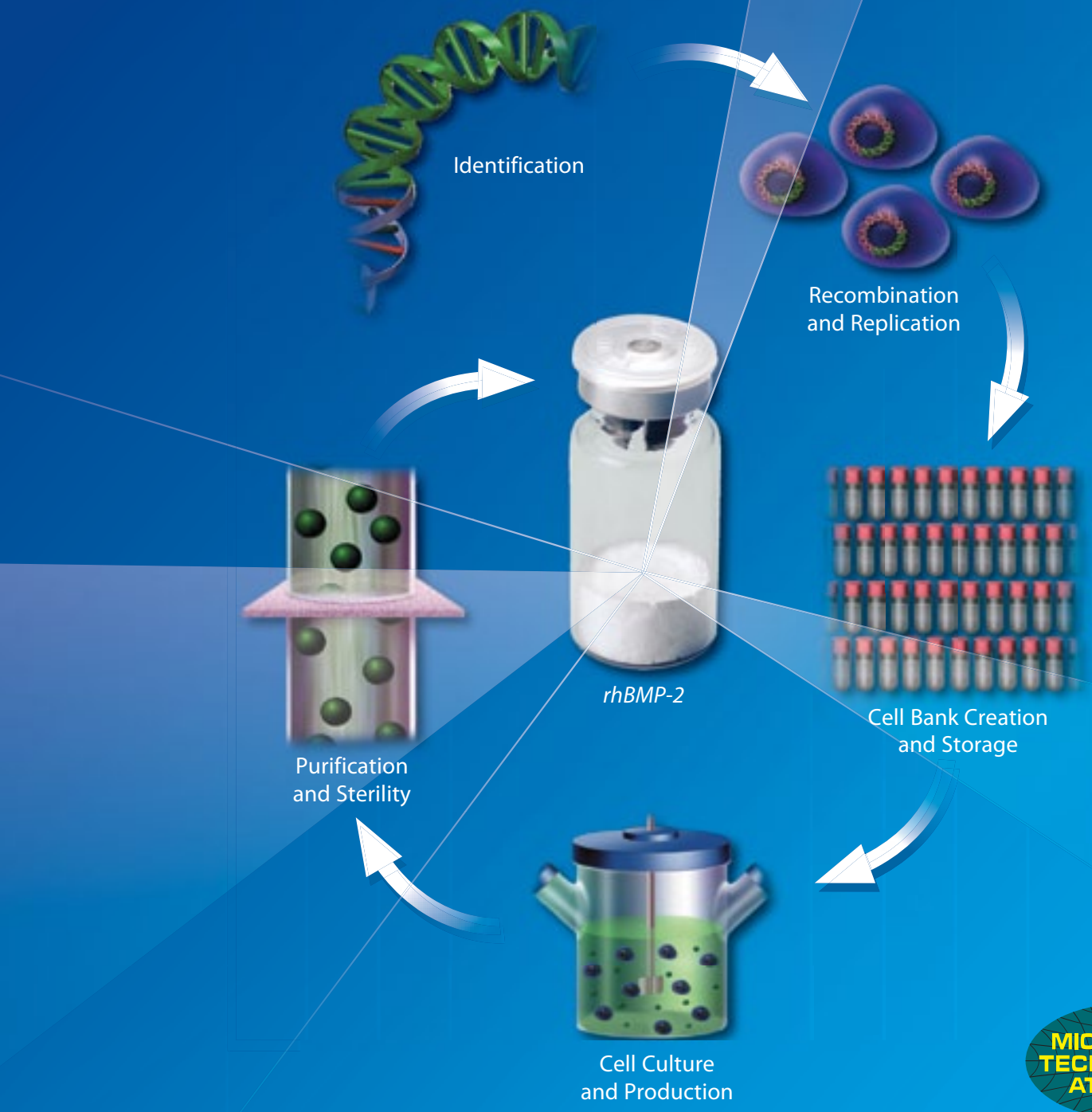
Medtronic

The Creation of rhBMP-2



MICHELSON TECHNOLOGY AT WORK

"BMP is destined to bring osteogenesis under the control of surgeons..."

Marshall R. Urist, MD, 1997

"The rhBMP-2 patients included in this analysis exhibited excellent fusion rates and improved clinical outcomes without the need for autogenous iliac crest bone graft."

Spine.2006;31(7):775-781.

"INFUSE® Bone Graft has more Level-1 clinical evidence than any other bone grafting material."

Resnick D, Dhoudhri T, Dailey A, et al. Guidelines for the performance of fusion procedures for degenerative disease of the lumbar spine. Part 16: bone graft extenders and substitutes. ***J Neurosurg Spine.*** June 2005;2:733–736.

INFUSE® BONE GRAFT

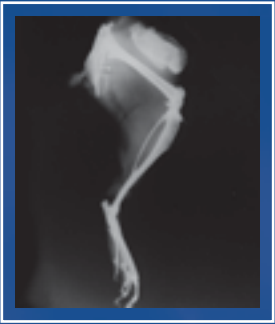
CONTAINS THE PROVEN, PREDICTABLE BONE-FUSING POWER OF

rhBMP-2

THE HISTORY OF rhBMP-2

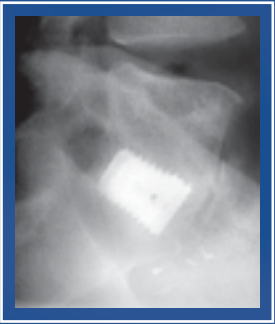
The history of rhBMP-2 stretches back for decades, providing a wealth of research and studies to support its ability to induce new bone formation.

1965



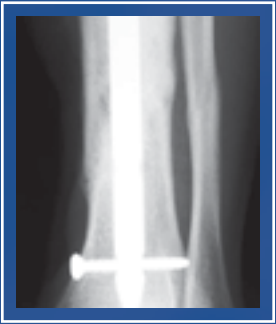
Dr. Marshall R. Urist discovers that demineralized bone matrix stimulates the formation of new bone tissue in lower-order animal muscle. This led to the isolation of bone morphogenetic proteins (BMP), the only proteins known to induce new bone formation (osteoinduction).

2002



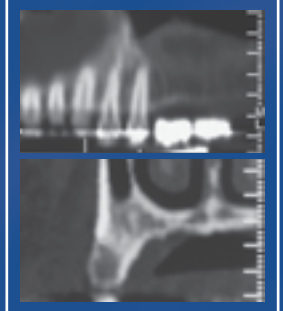
As a result of a prospective, randomized, clinical trial of 279 patients that proved rhBMP-2 to be equivalent to autograft, the U.S. Food and Drug Administration (FDA) approves INFUSE® Bone Graft/Medtronic Threaded Titanium Interbody Fusion Device for use in anterior lumbar spine fusion with certain interbody devices.

2004



After a prospective, randomized, clinical trial encompassing 299 patients, proving the healing power of rhBMP-2, INFUSE® Bone Graft gains FDA approval for open tibial fractures with intramedullary (IM) nail fixation.

2007



The FDA approves INFUSE® Bone Graft as an alternative to autogenous bone graft for sinus augmentations, and for localized alveolar ridge augmentations for defects associated with extraction sockets. This approval was based on data from 312 patients enrolled in a total of 5 clinical studies.

CREATING RECOMBINANT HUMAN BONE MORPHOGENETIC PROTEIN-2 (rhBMP-2)

The preferred method for obtaining BMP is to manufacture a recombinant version of a naturally occurring BMP using well-established molecular biology technique (e.g., recombinant insulin). This production method results in pure solutions of a single BMP. Recombinant production offers the advantage of tightly controlled manufacturing processes to ensure purity, consistency and sterility.

Using recombinant technology to develop and manufacture rhBMP-2 involves two phases:

Phase 1: Identifying, Replicating, and Storing the Human Gene for BMP-2

Phase 2: Producing, Purifying, Sterilizing and Validating rhBMP-2

Identification

Scientific breakthroughs at the Genetics Institute have led to the identification and isolation of the specific gene that carries the code for making Bone Morphogenetic Protein-2.

Cell Culture

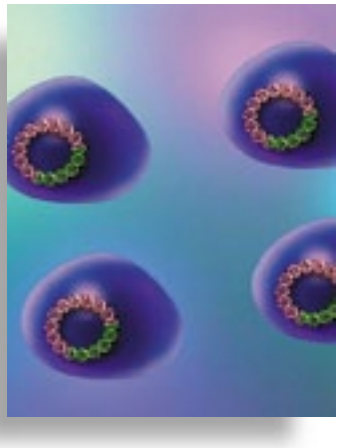
A vial of rhBMP-2 production cells is brought into the production room and placed into a glass "spinner flask." The spinner flask contains nutrients that the production cells need to grow and produce rhBMP-2. These nutrients, or "medium," contain a combination of vitamins, amino acids, minerals, and sugar, but they do not contain any human or animal components.

Phase 1: Identifying, Replicating, and Storing the Human Gene for BMP-2

Recombination

Once the gene was isolated, it was spliced and recombined into the DNA of a commonly used mammalian cell. "Recombinant" refers to the insertion, or recombination, of the gene into the production cell.

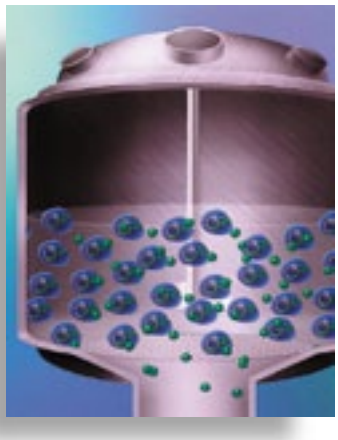
Replication



As the recombined cells grow and multiply, they include the new gene in their DNA. This replication process results in the development of a homogeneous population of cells capable of producing recombinant human Bone Morphogenetic Protein-2—rhBMP-2.

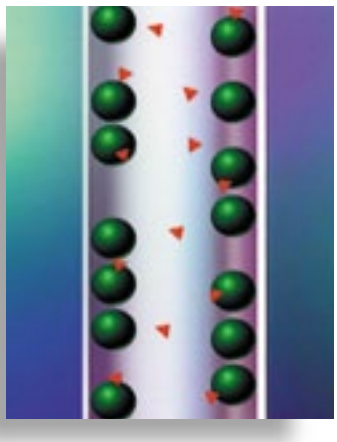
Phase 2: Producing, Purifying, Sterilizing and Validating rhBMP-2

Production



To foster cellular replication and production of rhBMP-2, they are transferred to a bioreactor, a computer-controlled, closed-system environment where large-scale production of rhBMP-2 begins. After a growth period of about three days, the recombined cells are filtered away from the rhBMP-2 containing medium and discarded. The rhBMP-2 moves on to the purification process.

Purification

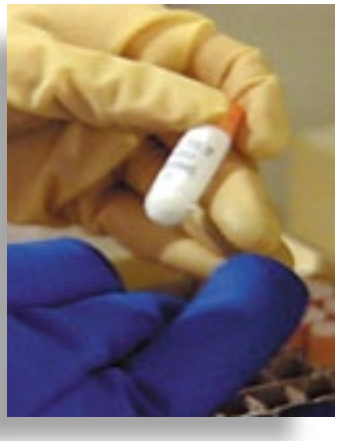


The purification process involves a series of four chromatography columns.

Cell Bank Creation

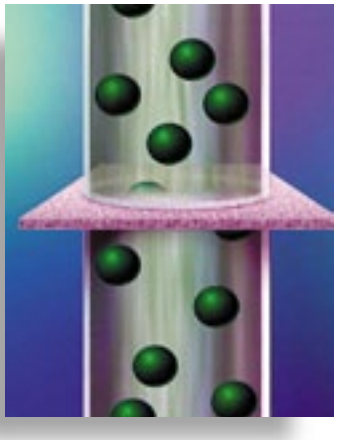
A single batch of rhBMP-2 production cells is grown and distributed into several hundred small vials, called a "cell bank." The cell bank is the source for all future production of rhBMP-2.

Cell Bank Storage



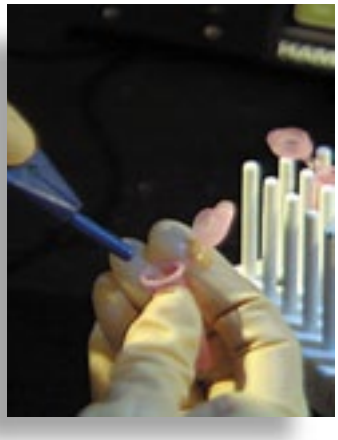
To safely maintain the cells until they are needed for rhBMP-2 production, the small vials are frozen at -135°C and stored in secure, monitored, temperature-controlled freezers. Because only a few recombined cells are needed to make many millions of rhBMP-2 units and future cell banks, the isolation and cloning process will not need to be repeated.

Sterility



For added viral safety assurance, a nano filtration step is included, even though no human or animal components are added during the recombinant production process.

Quality Validation



Throughout the production process, quality control testing is done to assess the safety, consistency and purity of all materials. A large number of tests are completed during the manufacture of rhBMP-2. Quality-checked liquid rhBMP-2 is filtered and freeze-dried in vials and then further tested for purity and consistency.

Advantages of the Recombinant Process to make rhBMP-2

- Sterile product
- >98% pure protein
- Constant supply
- Controlled production process
- Quality assurance, highly regulated
- Excellent safety profile
- Reproducible bioactivity

The purified rhBMP-2 is freeze-dried in vials. The vials are assembled into INFUSE® Bone Graft Kits.

Availability of rhBMP-2 Technologies

INFUSE® Bone Graft – Kit Components

Part Number/ Size	7510050 XX Small Kit	7510100 X Small Kit	7510200 Small Kit	7510400 Medium Kit	7510600 Large Kit	7510800 Large II Kit
INFUSE® Bone Graft Kit						
Total Graft Volume	0.7cc	1.4cc	2.8cc	5.6cc	8.0cc	8.0cc
Total mg rhBMP-2	1.05mg	2.1mg	4.2mg	8.4mg	12.0mg	12.0mg
Sterile Water for Injection	 (1) 5mL Vial	 (2) 5mL Vials	 (1) 5mL Vial	 (2) 5mL Vials	 (1) 10mL Vial	 (1) 10mL Vial
Sterile rhBMP-2	 (1) 1.05mg Vial	 (2) 1.05mg Vials	 (1) 4.2mg Vial	 (2) 4.2mg Vials	 (1) 12mg Vial	 (1) 12mg Vial
Sterile Absorbable Collagen Sponge (ACS)	 (1) ½" x 2" Sponge	 (1) 1" x 2" Sponge	 (2) 1" x 2" Sponges	 (4) 1" x 2" Sponges	 (6) 1" x 2" Sponges	 (1) 3" x 4" Sponge
PMA Approved Indication	Spine* Dental	Spine* Dental	Spine* Dental	Spine* Dental	Spine* Dental	Spine* Trauma Dental

*Must be used with a Medtronic Titanium Threaded Interbody Fusion Device.

BRIEF SUMMARY OF INDICATIONS, CONTRAINDICATIONS, AND WARNINGS FOR: INFUSE® BONE GRAFT/LT-CAGE® LUMBAR TAPERED FUSION DEVICE INFUSE® BONE GRAFT/INTER FIX™ THREADED FUSION DEVICE INFUSE® BONE GRAFT/INTER FIX™ RP THREADED FUSION DEVICE

The INFUSE® Bone Graft/Medtronic Titanium Threaded Interbody Fusion Device is indicated for spinal fusion procedures in skeletally mature patients with degenerative disc disease (DDD) at one level from L2-S1, who may also have up to Grade I spondylolisthesis or Grade 1 retrolisthesis at the involved level. The INFUSE® Bone Graft/ LT-CAGE® Lumbar Tapered Fusion Device is to be implanted via an anterior open or an anterior laparoscopic approach. INFUSE® Bone Graft with either the INTER FIX™ or INTER FIX™ RP Threaded Fusion Device is to be implanted via an anterior open approach.

The INFUSE® Bone Graft/Medtronic Titanium Threaded Interbody Fusion Device consists of two components containing three parts– a metallic spinal fusion cage, a recombinant human bone morphogenetic protein and a carrier/scaffold for the bone morphogenetic protein and resulting bone. **These components must be used as a system for the prescribed indication described above. The bone morphogenetic protein solution component must not be used without the carrier/scaffold component or with a carrier/scaffold component different from the one described in this document. The INFUSE® Bone Graft component must not be used without the Medtronic Titanium Threaded Interbody Fusion Device component.**

NOTE: The INTER FIX™ Threaded Fusion Device and the INTER FIX™ RP Threaded Fusion Device may be used together to treat a spinal level. LT-CAGE® Lumbar Tapered Fusion Device implants are not to be used in conjunction with either the INTER FIX™ or INTER FIX™ RP implants to treat a spinal level.

The INFUSE® Bone Graft/Medtronic Titanium Threaded Interbody Fusion Device is contraindicated for patients with a known hypersensitivity to recombinant human Bone Morphogenetic Protein-2, bovine Type I collagen or to other components of the formulation and should not be used in the vicinity of a resected or extant tumor; in patients with any active malignancy or patients undergoing treatment for a malignancy; in patients who are skeletally immature; in pregnant women; or in patients with an active infection at the operative site or with an allergy to titanium or titanium alloy.

There are no adequate and well-controlled studies in human pregnant women. In an experimental rabbit study, rhBMP-2 has been shown to elicit antibodies that are capable of crossing the placenta. Women of child bearing potential should be warned by their surgeon of potential risk to a fetus and informed of other possible orthopedic treatments. The safety and effectiveness of this device has not been established in nursing mothers. Women of child-bearing potential should be advised to not become pregnant for one year following treatment with this device.

Please see the package insert for the complete list of indications, warnings, precautions, adverse events, clinical results, definition of DDD, and other important medical information. The package insert also matches the sizes of those sized devices that are indicated for use with the appropriate INFUSE® Bone Graft kit.

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician with appropriate training or experience.

BRIEF SUMMARY OF INDICATIONS, CONTRAINDICATIONS, WARNINGS, AND PRECAUTION FOR INFUSE® BONE GRAFT FOR CERTAIN ORAL MAXILLOFACIAL AND DENTAL REGENERATIVE USES

INFUSE® Bone Graft is indicated as an alternative to autogenous bone graft for sinus augmentations, and for localized alveolar ridge augmentations for defects associated with extraction sockets.

The INFUSE® Bone Graft consists of two components – recombinant human Bone Morphogenetic Protein-2 (rhBMP-2) placed on an absorbable collagen sponge (ACS).

These components must be used as a system for the prescribed indication. The bone morphogenetic protein solution component must not be used without the carrier/scaffold component or with a carrier/scaffold component different from the one described in the package insert.

INFUSE® Bone Graft is contraindicated for patients with a known hypersensitivity to recombinant human Bone Morphogenetic Protein-2, bovine Type I collagen or to other components of the formulation and should not be used in the vicinity of a resected or extant tumor, in patients with any active malignancy or patients undergoing treatment for a malignancy, in pregnant women, or patients with an active infection at the operative site.

There are no adequate and well-controlled studies in human pregnant women. In an experimental rabbit study, rhBMP-2 has been shown to elicit antibodies that are capable of crossing the placenta. Women of child bearing potential should be warned by their surgeon of potential risk to a fetus and informed of other possible dental treatments. The safety and effectiveness of this device has not been established in nursing mothers. Women of child-bearing potential should be advised to not become pregnant for one year following treatment with this device.

INFUSE® Bone Graft has not been studied in patients who are skeletally immature (<18 years of age or no radiographic evidence of epiphyseal closure).

Please see the package insert for the complete list of indications, warnings, precautions, adverse events, clinical results, and other important medical information.

BRIEF SUMMARY OF INDICATIONS, CONTRAINDICATIONS, AND WARNINGS FOR: INFUSE® BONE GRAFT

INFUSE® Bone Graft is indicated for treating acute, open tibial shaft fractures that have been stabilized with IM nail fixation after appropriate wound management. INFUSE® Bone Graft must be applied within 14 days after the initial fracture. Prospective patients should be skeletally mature. INFUSE® Bone Graft consists of two components – recombinant human Bone Morphogenetic Protein-2 solution and a carrier/scaffold for the bone morphogenetic protein solution and resulting bone. **These components must be used as a system. The bone morphogenetic protein solution component must not be used without the carrier/scaffold component or with a carrier/scaffold component different from the one described in this document.**

INFUSE® Bone Graft is contraindicated for patients with a known hypersensitivity to recombinant human Bone Morphogenetic Protein-2, bovine Type I collagen or to other components of the formulation and should not be used in the vicinity of a resected or extant tumor, in patients with an active malignancy or patients undergoing treatment for a malignancy. INFUSE® Bone Graft should also not be used in patients who are skeletally immature, in patients with an inadequate neurovascular status, in patients with compartment syndrome of the affected limb, in pregnant women, or in patients with an active infection at the operative site.

There are no adequate and well controlled studies in human pregnant women. In an experimental rabbit study, rhBMP-2 has been shown to elicit antibodies that are capable of crossing the placenta. Women of child bearing potential should be warned by their surgeon of potential risk to a fetus and informed of other possible orthopedic treatments. The safety and effectiveness of this device has not been established in nursing mothers. Women of child-bearing potential should be advised to not become pregnant for one year following treatment with this device.

Please see the package insert for the complete list of indications, warnings, precautions, adverse events, clinical results, and other important medical information.

CAUTION: Federal (USA) law restricts this device to sale by or on the order of a physician with appropriate training or experience.

www.sofamordanek.com

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The surgical technique shown is for illustrative purposes only. The technique(s) actually employed in each case will always depend upon the medical judgment of the surgeon exercised before and during surgery as to the best mode of treatment for each patient. Please see the package insert for the complete list of indications, warnings, precautions, and other medical information.

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