CERAPEDICS

Enhancing the Science of Bone Repair

Cerapedics Announces ISASS Bone Grafting Policy Statement Features i-FACTOR™ Peptide Enhanced Bone Graft

ISASS (The International Society for the Advancement of Spine Surgery) recently put out a recommendation on bone graft substitutes where i-FACTOR™ was specifically categorized as drug/device combination in the same category as rhBMP-2.

The i-FACTOR™ peptide enhanced bone graft is manufactured and distributed by Cerapedics. This article discusses some uses that have not been approved by FDA. Please see attached pre-market approval letter from the FDA (Page 2), stating i-FACTOR's indication for use.

This article contains coding information to be used in connection with certain procedures associated with bone grafts. These codes are provided for informational purposes only and are not intended to apply to any particular situation. Nor are they intended to increase or maximize reimbursement by any payer. Providers are responsible for submitting the codes that most accurately describe the patient's medical condition, procedures performed, and products used as required by the payer's reimbursement policies. The information provided represents no promise or guarantee by Cerapedics regarding coverage or payment and may not be used as an official source of information.

For more information about the ISASS bone grafting policy statement you can read our press release – Click Here and see journal article below (Page 8).

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

November 3, 2015

Cerapedics, Incorporated
Mr. Roger N. White
Clinical and Regulatory Affairs
11025 Dover Street Suite 1600
Westminster, Colorado 80021

Re: P140019
i-FACTOR™ Peptide Enhanced Bone Graft
Filed: August 27, 2014
Amended: February 13, May 20, and June 9, 2015
Procode: NOX

Dear Mr. White:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your premarket approval application (PMA) for the i-FACTOR™ Peptide Enhanced Bone Graft. This combination product is indicated for use in skeletally mature patients for reconstruction of a degenerated cervical disc at one level from C3-C4 to C6-C7 following single-level discectomy for intractable radiculopathy (arm pain and/or a neurological deficit), with or without neck pain, or myelopathy due to a single-level abnormality localized to the disc space, and corresponding to at least one of the following conditions confirmed by radiographic imaging (CT, MRI, X-rays): herniated nucleus pulposus, spondylosis (defined by the presence of osteophytes), and/or visible loss of disc height as compared to adjacent levels, after failure of at least 6 weeks of conservative treatment. i-FACTOR™ Peptide Enhanced Bone Graft P-15 Putty must be used inside an allograft bone ring and with supplemental anterior plate fixation. We are pleased to inform you that the PMA is approved. You may begin commercial distribution of the device in accordance with the conditions of approval described below.

The sale and distribution of this device are restricted to prescription use in accordance with 21 CFR 801.109 and under section 515(d)(1)(B)(ii) of the Federal Food, Drug, and Cosmetic Act (the act). The device is further restricted under section 515(d)(1)(B)(ii) of the act insofar as the labeling must specify the specific training or experience practitioners need in order to use the device. FDA has determined that these restrictions on sale and distribution are necessary to provide reasonable assurance of the safety and effectiveness of the device. Your device is therefore a restricted device subject to the requirements in sections 502(q) and (r) of the act, in addition to the many other FDA requirements governing the manufacture, distribution, and marketing of devices.

Expiration dating for this device has been established and approved at 3 years. This is to advise you that the protocol you used to establish this expiration dating is considered an approved protocol for the purpose of extending the expiration dating as provided by 21 CFR 814.39(a)(7).

Continued approval of this PMA is contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA. Two copies of this report, identified as "Annual Report" and bearing the applicable PMA reference number, should be submitted to the address below. The Annual Report should indicate the beginning and ending date of the period covered by the report and should include the information required by 21 CFR 814.84. This is a reminder that as of September 24, 2014, class III devices are subject to certain provisions of the final UDI rule. These provisions include the requirement to provide a UDI on the device label and packages (21 CFR 801.20), format dates on the device label in accordance with 21 CFR 801.18, and submit data to the Global Unique Device Identification Database (GUDID) (21 CFR 830 Subpart E). Additionally, 21 CFR 814.84 (b)(4) requires PMA annual reports submitted after September 24, 2014, to identify each device identifier currently in use for the subject device, and the device identifiers for devices that have been discontinued since the previous periodic report. It is not necessary to identify any device identifier discontinued prior to December 23, 2013. For more information on these requirements, please see the UDI website, http://www.fda.gov/udi.

In addition to the above, and in order to provide continued reasonable assurance of the safety and effectiveness of the device, the Annual Report must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device.

You have agreed to the following product stability requirements with the reports submitted separately from the annual reporting requirement:

1. Conduct bioactivity stability test for the first 3 production batches of i-FACTOR™ Peptide Enhanced Bone Graft product manufactured and packaged according to the commercialized manufacturing process. The stability study should be performed at the long term controlled storage condition of 25°C/60%RH with test frequency of 0, 6, 12 months for the 1st year, every 6 months for the 2nd year and annually thereafter through the shelf life. The stability data report should be submitted as a "Report – Other" due at the same time as the annual report, but submitted separately from the annual report.

2. Place a minimum one commercial batch of the finished product into long-term stability testing at 25°C/60% RH through the shelf life on an annual basis if manufactured.

3. Withdraw from the market, any batches that fail to meet the approved specifications for the putty product during long-term stability evaluations.

In addition to the Annual Report requirements, you must provide the following data in post-approval study (PAS) reports for each PAS listed below. Separate PAS Progress Reports must be submitted for each study every six (6) months during the first two (2) years of the study and annually thereafter, unless otherwise specified by FDA. Two (2) copies of each report, identified

as an "ODE Lead PMA Post-Approval Study Report" in accordance with how the study is identified below and bearing the applicable PMA reference number, should be submitted to the address below.

ODE Lead PMA Post-Approval Study – i-FACTOR™ Peptide Enhanced Bone Graft Continuation Study: The Office of Device Evaluation (ODE) will have the lead for this clinical study, which was initiated prior to device approval. The i-FACTOR™ Peptide Enhanced Bone Graft Continuation Study is a continuation of the collection of data from subjects who were enrolled in the clinical study used to support approval of the PMA. The purpose of the study is to collect longer-term data describing the safety and effectiveness of the identified product. The clinical and radiographic endpoints identified in the original protocol (included in Attachment IV-4.6 of the original PMA submission) will continue to be collected annually until each subject has had a total of six years' worth of data collected.

It is expected that 220 total subjects will be enrolled in the study. A conservative estimate of expected number of subjects at 6 years follow-up is 170 subjects (*i.e.* loss of 10 subjects per year due to withdrawals, death and other causes). Further, a follow-up rate of up to 70% is expected at all follow-ups. Thus, data from a total of 154 subjects are expected to be available at year 3 and from 120 subjects at year 6.

The working study hypothesis is that i-FACTOR™ Peptide Enhanced Bone Graft will be non-inferior to autologous bone. This working hypothesis will be tested by a non-inferiority approach as follows. In order to be a success, non-inferiority structured H0 for each primary efficacy endpoint has to be rejected. Three independent hypotheses will be tested, for each of the primary endpoints using the same non-inferiority margins as in the main study. The hypotheses will be tested with one-sided and two-sided 95% C.I. For the fusion and neurological success primary endpoints, the exact binomial confidence interval will be created. For the change in NDI primary endpoint, the confidence intervals for the differences in mean change between the groups adjusting for baseline NDI value will be created. If the confidence interval does not include non-inferiority margin, the H0 will be rejected. An evaluation for the need to adjust the analysis for possible differences between the groups will be included.

Statistical power:

- It is estimated that the fusion rate will be between 98% and 100% at all follow-ups based on the main study results. At 3 years, the study will have 99% power and at 6 years it will have 98% power to reject non-inferiority H0 with non-inferiority margin of 10%.

- The study will have 97% power at 3 years and 93% power at 6 years to reject H0 for the change in NDI outcome under the standard deviation assumption of 19 (based on the main study) and a non-inferiority margin of 11.

- The study will have 95% power at 3 years and 90% power at 6 years to reject non-inferiority H0 for neurological success outcome under the assumption of a neurological success rate of 93% as observed in the main study and a non- inferiority margin of 15%.

The rate of adverse events will be compared between the i-FACTOR™ Peptide Enhanced Bone Graft and the control arm using the Fisher exact test and superiority approach, in the same way as in the original IDE study. Failure to reject H0 or, rejection of H0 in favor of i-FACTOR™ Peptide Enhanced Bone Graft group will meet safety success. The rate of subsequent surgical interventions at the index level will also be compared.

The data from this study will be submitted as part of the annual report and will include the following data collected annually for each subject:

1. a description of any surgical interventions, which will include reoperations, removals, revisions, and supplemental fixations;

2. a radiographic assessment of fusion using the same criteria employed in the original IDE study;

3. an assessment of neurological outcomes;

4. an assessment of pain and function using the same criteria employed in the original IDE study (*i.e.*, change in NDI and change in neck and arm VAS for pain); and

5. other primary and secondary endpoints not specified in items 1-3 above, as specified in the IDE study protocol addendum.

Be advised that the failure to conduct any such study in compliance with the good clinical laboratory practices in 21 CFR part 58 (if a non-clinical study subject to part 58) or the institutional review board regulations in 21 CFR part 56 and the informed consent regulations in 21 CFR part 50 (if a clinical study involving human subjects) may be grounds for FDA withdrawal of approval of the PMA. In addition, the results from any post approval study should be included in the labeling as these data become available. Any updated labeling must be submitted to FDA in the form of a PMA Supplement. For more information on post-approval studies, see the FDA guidance document entitled, "Procedures for Handling Post-Approval Studies Imposed by PMA Order" (http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm070974.htm).

Within 30 days of your receipt of this letter, you must submit a PMA supplement that includes a complete protocol of your post-approval study described above. Your PMA supplement should be clearly labeled as an "ODE Lead" as noted above and submitted in triplicate to the address below. Please reference the PMA number above to facilitate processing. If there are multiple

protocols being finalized after PMA approval, please submit each protocol as a separate PMA supplement.

Before making any change affecting the safety or effectiveness of the device, you must submit a PMA supplement or an alternate submission (30-day notice) in accordance with 21 CFR 814.39. All PMA supplements and alternate submissions (30-day notice) must comply with the applicable requirements in 21 CFR 814.39. For more information, please refer to the FDA guidance document entitled, "Modifications to Devices Subject to Premarket Approval (PMA) - The PMA Supplement Decision-Making Process" (www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089274.htm).

You are reminded that many FDA requirements govern the manufacture, distribution, and marketing of devices. For example, in accordance with the Medical Device Reporting (MDR) regulation, 21 CFR 803.50 and 21 CFR 803.52, you are required to report adverse events for this device. Manufacturers of medical devices, including in vitro diagnostic devices, are required to report to FDA no later than 30 calendar days after the day they receive or otherwise becomes aware of information, from any source, that reasonably suggests that one of their marketed devices:

1. May have caused or contributed to a death or serious injury; or

2. Has malfunctioned and such device or similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Additional information on MDR, including how, when, and where to report, is available at www.fda.gov/MedicalDevices/Safety/ReportaProblem/default.htm.

In accordance with the recall requirements specified in 21 CFR 806.10, you are required to submit a written report to FDA of any correction or removal of this device initiated by you to: (1) reduce a risk to health posed by the device; or (2) remedy a violation of the act caused by the device which may present a risk to health, with certain exceptions specified in 21 CFR 806.10(a)(2). Additional information on recalls is available at www.fda.gov/Safety/Recalls/IndustryGuidance/default.htm.

CDRH does not evaluate information related to contract liability warranties. We remind you; however, that device labeling must be truthful and not misleading. CDRH will notify the public of its decision to approve your PMA by making available, among other information, a summary of the safety and effectiveness data upon which the approval is based. The information can be found on the FDA CDRH Internet HomePage located at www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/default.htm. Written requests for this information can also be made to the Food and Drug Administration, Dockets Management Branch, (HFA-305), 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. The written request should include the PMA number or docket

number. Within 30 days from the date that this information is placed on the Internet, any interested person may seek review of this decision by submitting a petition for review under section 515(g) of the act and requesting either a hearing or review by an independent advisory committee. FDA may, for good cause, extend this 30-day filing period.

Failure to comply with any post-approval requirement constitutes a ground for withdrawal of approval of a PMA. The introduction or delivery for introduction into interstate commerce of a device that is not in compliance with its conditions of approval is a violation of law.

You are reminded that, as soon as possible and before commercial distribution of your device, you must submit an amendment to this PMA submission with copies of all approved labeling in final printed form. Final printed labeling that is identical to the labeling approved in draft form will not routinely be reviewed by FDA staff when accompanied by a cover letter stating that the final printed labeling is identical to the labeling approved in draft form. If the final printed labeling is not identical, any changes from the final draft labeling should be highlighted and explained in the amendment.

All required documents should be submitted in 6 copies, unless otherwise specified, to the address below and should reference the above PMA number to facilitate processing.

U.S. Food and Drug Administration
Center for Devices and Radiological Health
PMA Document Control Center – WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

If you have any questions concerning this approval order, please contact Aric Kaiser at 301-796-6425 or aric.kaiser@fda.hhs.gov.

Sincerely yours,

Mark N. Melkerson -S

Mark N. Melkerson
Division Director
Division of Orthopaedic Devices
Office of Device Evaluation
Center for Devices and Radiological Health

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ISASS Recommendations and Coverage Criteria for Bone Graft Substitutes used in Spinal Surgery

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ABSTRACT

Autologous bone graft remains the gold standard by which bone graft substitutes are compared in spine fusion surgery. The utilization of bone graft substitutes, either as (1) an extender for spinal fusion constructs or (2) an alternative to minimize morbidity while maximizing outcomes, is changing. Moreover, current procedures technology (CPT) code 20939 became effective in 2018 defining bone marrow aspirate for bone grafting, spine surgery only. Changes in the complex landscape of grafting materials have prompted ISASS to provide category guidance for bone graft substitutes by comparing and contrasting US regulatory pathways, mechanisms of action, and supportive clinical evidence for these bone grafting materials.

Testing & Regulatory Affairs

INTRODUCTION

Over the past 3 decades, there has been an increased interest in bone grafting materials as these materials have become a vital part of most spinal procedures. Unlike other areas of orthopedics, spinal surgery often requires grafting procedures to induce de novo bone in an area stabilized by metal devices. When considering potential graft materials, assuming an adequate blood supply, it is important to note that a successful graft needs to have at least 2 of the following: cells, signal, and/or matrix. *Cells* refers to the process of osteogenesis that is defined as cellular formation of new bone. These are dedicated cells in the area of the graft, such as osteoblasts or stem cells, that enter the osteoblastic lineage and ultimately form new bone. The *signal*, or osteoinduction, is orchestrated by bioactive molecules, primarily low-molecular-weight members of the transforming-growth-factor–β family that actively recruit mesenchymal cells, and stimulate them to differentiate into bone-forming cells for osseous repair. The *matrix* is the scaffolding that permits cell infiltration and in-growth of new host bone that is referred to as osteoconduction. The combination of these properties can either come from materials introduced to the site or those recruited from the host.

When evaluating the complex landscape of grafting materials, it is difficult to compare the options as the regulatory pathways, mechanisms of action, and supportive clinical evidence of the materials vary widely. In the 1990s, demineralized bone matrix (DBM) and synthetic bone grafts became widely available. Whereas DBMs were initially classified as tissue product and not a medical device, synthetics were classified as medical devices subject to the 510(k) pathway. In 2006, the regulatory pathway significantly changed in the United States regarding DBMs, with the Food and Drug Administration (FDA) reclassifying versions of DBMs with a non-tissue carrier to require 510(k) clearance, while leaving pure DBM versions exempt as human tissue products. Further, in 2001, the first Class III medical device grafting material was approved by the FDA, bone morphogenetic protein (BMP)-2. In the mid-2000s, annual sales of BMP-2 rose to approach $900 million per year, but, in response to new data and the medico-legal concerns, revenues declined to less than $450 million annually in 2017. Lastly, an area almost nonexistent a decade ago has now gained almost 10% of the market: cell-based matrices. These matrices are a broad category of materials marketed as human cell or tissue products (HCT/Ps) claimed to contain stem cells and related factors. (Note: HCT/P status requires that the market product's mechanism of action not "be dependent on the metabolic activity of living cells.")

Although autologous bone grafting (ABG), most commonly from the iliac crest or local bone, is the

Table 1. Safety and efficacy of bone graft substitutes.

Category	Regulatory Pathway	Mechanism of Action	Available Data
Nonstructural allografts	HCT/P	Osteoconduction: matrix	No premarket data review by FDA. Long-standing clinical experience, reasonable body of literature
Demineralized bone grafts	510(k) as autograft extender in PLF	Osteoconduction, theoretical osteoinduction: matrix, signals?	Animal study for 510(k) clearance, limited clinical studies
Cellular-based allografts	HCT/P*	Osteoconduction, theoretical osteoinduction: matrix, signals?	No premarket data review by FDA, very limited preclinical and clinical studies
Synthetic bone grafts	510(k) as autograft extender in PLF	Osteoconduction: matrix	Animal study for 510(k) clearance, limited clinical studies
Autologous cellular grafts	510(k) for the concentration devices	Osteogenesis: cells	In vitro data for 510(k), limited clinical studies
Class III, drug-device combination products	IDE/PMA as stand-alone autograft replacements	BMP-2 osteoinductivity P-15 cellular attachment and activation	Level I IDE human clinical study required for PMA approval.

Abbreviations: HCT/P, human cell or tissue product; FDA, Food and Drug Administration; PLF, posterolateral fusion; IDE, investigational device exemption; PMA, premarket approval; BMP, bone morphogenetic protein.
*HCT/P status requires that the market product's mechanism of action not "be dependent on the metabolic activity of living cells."

classical standard, this guidance focuses on the alternatives to ABG. This guidance is separated into 6 major categories: (1) nonstructural allograft, (2) demineralized bone grafts, (3) cellular allografts, (4) synthetic bone grafts, (5) autologous cellular grafts, and (6) Class III, drug-device combination products (Table 1).

US Regulatory Pathways for Bone Graft Products

The required regulatory pathways by which bone graft products get to market, and the required data to support those pathways are varied.

Human Cell or Tissue Products

The US Code of Federal Regulations Title 21, part 1271 (Human Cells, Tissues, and Cellular and Tissue-Based Products), contains all of the regulations related to materials covered by these regulations. Section 361 describes products that are minimally manipulated, are for homologous use only, do not have a systemic effect, and are not dependent on the metabolic activity of living cells for their primary function, in addition to other qualifications. Once a manufacturer determines a product meets all of these requirements and follows the appropriate regulations, the manufacturer can place the product on the market by simply notifying the FDA of the intent to do so. There is no premarket review by the FDA for safety or efficacy of such products and, therefore, there are no requirements for preclinical or clinical data.

Section 510(k)

Section 510(k) of the Federal Food, Drug, and Cosmetic Act describes a regulatory process for the clearance of products meeting certain requirements that have been demonstrated to the FDA's satisfaction to be "substantially equivalent" in safety and effectiveness to another lawfully marketed device when used for the same purpose. In the case of bone graft materials, there are currently 2 options for 510(k) clearance for materials used in the extremities and pelvis or for the spine. For the extremities label, the FDA requires a drill-hole defect model in animals comparing the new device to the predicate. For the spine label, the FDA requires a rabbit posterolateral fusion model. With a 510(k) for the spine, the product is cleared for use as an autograft extender in posterolateral fusion. The manufacturer can choose to conduct postmarket clinical studies but is under no obligation to do so. There are currently 398 510(k) clearances for bone graft products.

Premarket Approval

The premarket approval (PMA) pathway is the most stringent and is required for Class III medical devices. In bone grafting, the drug-device combination products have been required to utilize this pathway to market. The PMA pathway is based on demonstration of safety and effectiveness through "adequate and well-controlled" clinical trials. The required trials are done under FDA supervision in the form of an investigational device exemption (IDE) in which the study design, outcome measures, etc., are approved by the FDA prior to initiation of the study. As these are level 1 clinical studies, the data from them can be relied upon in making clinical use decisions.

NONSTRUCTURAL ALLOGRAFTS

Brief History

Nonstructural allografts have been commonly used in modern medicine since the late 19th century. With the establishment of US bone banks in the 1940s and rapid expansion in the 1980s, the availability and utilization of this graft material has been readily accepted in bone healing procedures to fill large osseous defects. It is the most commonly used form of nonautologous bone grafting. The American Association of Tissue Banks (AATB) was founded in 1976 by a group of doctors and scientists who had previously founded the US Navy Tissue Bank. The AATB is an association comprised of more than 120 tissue banks and individual members dedicated to promoting the safety, quality, and availability of donated human tissue. Following AATB accredited guidelines, allograft material is harvested from human cadaveric bone, processed, stored, and transplanted to a recipient. It is widely recognized as an alternative to autogenous bone. Available in bulk, nonstructural allograft bone is provided as either fresh-frozen or freeze-dried in 2 product forms as cancellous or cortical material.

Cancellous allograft provides little mechanical strength and is primarily used to pack and fill bony voids.

Cortical allograft can provide some semistructural properties for certain applications in conjunction with supportive hardware. They are used to fill large osseous defects or in interbody spinal fusions.

Science

The advantage of animal studies in elucidating the science and effects of bone grafting materials includes testing the mechanical properties. Jensen et al. found that allograft bone produced an early implant fixation and bone incorporation.[1] Nguyen et al[2] studied the sterilization of allograft bone by gamma irradiation and its effect on allograft biology and biomechanics. The effects varied between different doses and have not been studied in clinical trials but include possible effects on remodeling.

Regulatory Pathway

Nonstructural allografts are regulated as HCT/Ps, and manufacturers are not required to provide preclinical or clinical data prior to the introduction into commercial use. The emphasis of HCT/P regulation is product safety with a focus on donor screening and blood testing. These materials are aseptically processed, and many are also terminally sterilized (ie, with gamma radiation) to ensure safety.

Mechanism of Action

Being biologically inactive, nonstructural allografts are neither osteogenic nor osteoinductive. They are used as bone graft substitutes due to their osteoconductive properties, which provide an inert scaffold for fusion to occur. The allograft bone is then incorporated and resorbed and replaced.[3]

Clinical Evidence

The clinical evidence is broad and covers sinus augmentation, tibial fractures, and spine fusion. Betz et al[4] conducted a prospective randomized study for posterior spinal fusion with 37 patients receiving allografts and 39 patients receiving no bone grafting. The allograft results after 24 months indicated that success was achieved without autogenous bone graft. Avila et al. used allograft bone as the only fusion material in 20 patients and 39 implants.[5] Clinical and histologic findings support the use of cortical and cancellous allograft in sinus augmentation procedures. Jones et al[6] also studied posterior fusion for pediatric idiopathic scoliosis with blinded radiologists evaluating 55 patients. Fusion success was 92.7% and loss of curve correction of 4.4 degrees after a minimum of 24 months. Tibial plateau fractures were studied by Lasanianos et al[7] with 23 patients with average follow-up of 13 months. The allograft was soundly incorporated in all cases within 12 weeks from surgery. A systematic review comparing allograft to autograft in lumbar fusion was performed by Liao et al.[8] One randomized controlled study, 1 prospective study, and 2 retrospective studies resulted in 333 patients with allografts and 175 with autografts. The change of Oswestry Disability Index (ODI) and visual analog scale (VAS) pain scores at 1, 2, and 3 years were similar as were the fusion rates ($P > .05$ for the 3 outcomes).

In conclusion, nonstructural allografts are safe, accepted, biologically inert bone grafts. The lack of donor site morbidity, general success of outcomes, and decreased surgical times make allograft bone a popular alternative to autologous bone graft.

Although the risks are low they could include viral transmission and host rejection. The clinical evidence is broad and inconclusive across a variety of surgical applications. The osteoconductive nature of this bone product lends itself to applications where bulk and mass are needed to fill a bony defect and to act as an extender of local autograft in a fusion bed.

DEMINERALIZED BONE GRAFTS

Brief History

Demineralized bone was first described by Urist.[9] Although the potential of DBM was discovered almost 40 years ago, it has only been clinically available since the early 1990s. With an increased demand by surgeons for allograft bone, the National Organ Transplant Act was passed to facilitate the development of tissue and organ donor networks (Public Law 98-507, 1984). In July 1997, the FDA released industry standards for donor screening, which are complemented by the American Association of Tissue Banks (AATB) requirements for screening, processing, and distribution procedures of all donors. In 2006, the FDA reclassified DBMs with carriers to be a Class II product requiring 510(k) approval. However, DBMs that do not have carriers are still considered HCT/Ps and are not regulated as devices.

Processing of DBM

A DBM is formed after a mild acid extraction of cadaveric bone that removes the mineral phase, leaving 90% to 95% collagen with the remaining noncollagenous proteins including proteoglycans, osteocalcin, osteopontin, bone sialoprotein, and trace amounts of BMPs. DBM offers the intrinsic properties of osteoconduction and potential osteoinduction due to the retained BMPs. The DBM powder or fibers are mixed with a carrier to provide better handling characteristics, and commercial DBMs are available as gels, putties, pastes, and fabrics that have been tailored to try to meet the needs of the surgical procedure.

There are a variety of processing methods used in products commercially available today, each with its own limitations. Treatment solutions, solvent concentrations, and chelating agents are all suspected of affecting the potential osteoinductivity of the DBM. Urist showed that hydrochloric acid, commonly used in DBM processing, mixed with alcohols produces noninductive DBM. Chelating agents such as EDTA have been shown to not fully demineralize the bone and reduce DBM performance.[10] Other processing factors that can affect the potency of resulting DBM are antibiotics, particle size, fiber size, temperature, calcium content, and sterilization method.[9,11,12]

Sterilization methods are probably one of the most widely diverse components of DBM processing. Many DBMs are produced under sterile conditions. Most are also terminally sterilized. There has been much published literature on all the different methods with the below serving as only an overview. Aseptic processing is the method of using sterile practices from recovery to packaging. It alleviates the need for end-term sterilization but is much more involved and expensive. Gamma irradiation has been shown to diminish or destroy the osteoinductive potential when used at levels of 2.0 mrad or higher.[13,14] Ethylene oxide has also been shown to reduce or eliminate osteoinductivity and can cause an inflammatory response from residuals.[14–17]

In summary, processing and sterilization techniques greatly affect the osteoinductivity of the product. The only accurate way to determine the osteoinductivity of the final product is to test it in the athymic rat (rnu/rnu) muscle pouch model.[9,18] Although in vitro methods are sometimes referenced as an acceptable methodology to determine osteoinductivity, these methods only show the potential to form new bone. Results using this model have been presented and show there is a wide range of osteoinductivity in current products.[19] It is also important to recognize that osteoinductivity in athymic rat or other models has not been correlated with efficacy in humans.

DBM Preclinical

Urist first described the potential for DBM to induce new bone formation.[9] He showed that DBM placed in a heterotopic muscle pouch could induce new bone formation in 28 days by endochondral ossification. Many studies since Urist's initial findings have proven the osteoinductive potential of DBM in various animal models.[20–23]

DBM has been shown efficacious in several spine fusion models.[21,22,24,25] Martin et al[23] demonstrated the importance of formulation tailored to procedure. Their results reveal fusion rates with fabric DBM sheets were superior to ABG, and putty forms were equivalent to ABG in a posterolateral rabbit

spine fusion model. Wang et al. studied the differences between 3 commercially available DBM putties (Osteofil, Grafton, and Dynagraft) with different processing using a posterolateral athymic rat model. Their results showed no statistically significant difference between the fusion rates of Osteofil and Grafton. None of the Dynagraft rats achieved fusion.[26] Recently, Brecevich et al. studied Accell Evo3 and Grafton in athymic rats in posterolateral lumbar fusion. They were assessed at either 3 weeks or 9 weeks to see the rate and efficacy of fusion. Both DBM-treated groups achieved a significantly higher rate of fusion than the ABG-treated group at 9 weeks in this model. Successful fusion was also demonstrated in the DBM-treated groups at 3 weeks.[27]

DBM Clinical

DBM has been used alone and to augment autogenous bone grafts in the repair of cysts, fractures, nonunions, and spine fusions. In several clinical situations, DBM has been used with considerable success. A recent retrospective review of patients who had undergone instrumented posterolateral lumbar spinal fusion with autogenous bone graft and Grafton Gel was performed by Sassard et al.[28] They compared Grafton Gel–implanted patients with an age-, gender-, and procedure-matched group of patients undergoing instrumented fusions with autografts harvested from the iliac crest. Using a bone mineralization rating scale, they did not find any radiographic differences between the groups based upon films taken 3, 6, 12, and 24 months after surgery. The fusion rates in the Grafton Gel with local bone group and the autograft group were 60% and 56%, respectively, statistically comparable. At 24 months, the fusion rates were less than had been reported in other studies of instrumented posterior fusion and were attributed to grading criteria. The choice of instrumentation was significantly related to fusion success and was the most important predictor of 24-month bone mineralization. In the first multicenter, prospective, clinical trial with DBM, the efficacy of DBM mixed with autograft was compared to autograft alone in posterolateral fusion with pedicle screw fixation of 120 patients.[29] Autogenous bone graft from the iliac crest was implanted in one of the lateral gutters of the spine and a Grafton DBM–iliac crest autograft composite was implanted on the contralateral side in the same patient. Fusion was achieved in 52% of the DBM-autograft sides and in 54% on the autograft side. Their conclusion was that Grafton DBM was a successful extender of autograft in spinal arthrodesis. It should be noted, though, that gel formulations are the oldest forms of DBMs and newer fabric forms have improved osteoconductivity and are more suitable for this indication. Recently, in a prospective multicenter randomized clinical trial, Kang et al. compared the outcomes of Grafton DBM with local bone against iliac crest bone graft (ICBG) in a single-level instrumented posterior lumbar fusion.[30] Forty-six patients were randomly assigned (2:1) to receive Grafton DBM with local autograft bone (30 patients) or autologous ICBG (16 patients). An independent radiologist evaluated plain radiographs and computed tomographic scans and 2-year time points reported fusion rates were not statistically different with the Grafton-autograft group at 86% versus the ICBG at 92%.

In summary, a commercial DBM has been shown to be successful as an autograft extender in posterolateral spinal fusion in clinical studies.

CELLULAR-BASED ALLOGRAFTS

Cellular autografts (CBMs) are comprised of a combination of osteoconductive carriers and cryopreserved allogeneic cells (generally mesenchymal stem cells [MSCs]). The carriers are bone-based materials such as cancellous bone chips or DBM that are routinely used in the clinical setting as osteoconductive bone graft products. These carriers provide inert scaffolding for the delivery of the cellular component of the CBM. The MSCs are derived from cadaveric bone, cadaveric adipose tissue, or live donor placental tissue.

The CBMs are marketed as HCT/Ps and, thus, are not required to provide preclinical or clinical data prior to the introduction into commercial use. The emphasis of HCT/P regulation is product safety as exemplified by donor screening. In addition, these products are not required to be terminally sterilized, like 510(k) or PMA products, but rely on aseptic processing to ensure safety.

The manufacturing process to produce the CBM products is proprietary and, thus, the exact procedures for the preparation of these materials are not available. In general, the cadaveric bone material is harvested at an accredited tissue bank by standard AATB accredited technique. Strict attention is made to preserve the cellular components of the bone

tissue, while the noncellular proteinous material is removed. The number of cells per milliliter are claimed to range from 66 000 to greater than 3 million.

CBMs are provided as frozen products and must be stored at –80°C. Therefore, they require a preimplantation thawing step. Neither the reproducibility of cell recovery, post-thaw, nor the viability of the cells following implantation has been established for these products.

The mechanism of action for the CBM is multifaceted. The manufacturers indicate that the CBM products are osteoconductive, osteoinductive, and osteogenic. Clearly, the use of the bone matrix materials as the inert carriers provides ample osteoconductive material. The presence of living cells theoretically provides bone growth factors to recruit cells and stimulate new bone formation. These effects have been demonstrated in benchtop and preclinical testing; however, limited clinical evidence of an osteoinductive effect has been published. The presence of living cells supports the idea of an osteogenic presence, though the postimplant viability of the implanted cells has not been established. The postimplantation generation of bone-stimulatory growth factors has not been established. The HCT/P classification does not require validation of the growth factor production for these products. Lot-to-lot cell composition is not required for an HCT/P product. Per FDA guidance documents on HCT/P products, they cannot "rely on the metabolic activity of living cells for their primary function," as this would render them biologic drugs (section 360) as opposed to HCT/Ps, which would require a biologic license application and clinical trials.

As HCT/P-regulated products, clinical data are not required for CBMs prior to commercialization. However, there are published results of clinical use of these products. McAnany et al. compared Osteocel CBM to a retrospective paired cohort of allograft patients in an anterior cervical discectomy and fusion (ACDF) surgery (n = 57 subjects/arm).[31] The CBM product yielded 87.7% fusion at 12 months, which was not statistically better than the allograft control arm (94.7% fusion). Eastlack et al. analyzed 182 patients implanted with OsteoCel in a noncontrolled ACDF study.[32] At 2 years, 92% of the subjects demonstrated fusion and an improvement in neck disability index (NDI) and VAS scores.

Vanichachorn et al[33] examined Trinity Evolution CBM in an uncontrolled ACDF study. The results demonstrated that the patients displayed significant improvement in NDI and VAS scores along with a fusion rate of 78.6% at 6 months and 93.5% at 12 months. These fusion outcomes are within the expected fusion results from standard allograft bone graft products. Peppers et al. performed a prospective, noncontrolled evaluation of Trinity Evolution in 40 ACDF patients.[34] At 12 months the fusion rate was 89.4%. Musante et al. performed a retrospective assessment of Trinity Evolution as a "bone graft extender" in posterolateral arthrodesis subjects.[35] At 12 months the fusion rate of 90.7% was established, which is considered equal to or better than ICBG. Divi et al[36] tested Vivigen in 21 patients for cervical fusion in an uncontrolled study. At 6 months all of the patients displayed fusion and improvement of NDI scores.

In conclusion, CBM represents a promising bone grafting technology, but the HCT/P regulatory classification allows for the introduction of products without FDA review of preclinical or human clinical data for safety and efficacy. In addition, the biological mechanism for new bone formation has not been well elucidated in the clinical setting. The postimplantation biology regarding cell viability, differentiation, immunogenicity, and the growth factor profile has not been established in rigorous clinical trials.

SYNTHETIC BONE GRAFTS

One of the essential elements of bone regeneration is osteoconduction, which provides a scaffold (matrix) for the progenitor cells to proliferate and differentiate. Besides providing support as a structural lattice, optimal osteoconductive materials must be resorbable such that they can be remodeled along with the newly formed bone. The synthetic bone grafts currently used in spine are generally tricalcium phosphate (TCP, hydroxyapatite, or combinations of the 2. These osteoconductive compounds have been favored because they elicit very little immunologic reaction in adjacent tissues and have negligible systemic toxicity. The FDA currently allows for 2 different approaches for 510(k) clearance of synthetic bone grafts, for use in "extremities and pelvis," or "spine" on the basis of different animal study requirements. To achieve a clearance for extremities, the sponsor is expected to provide data from a long bone drill defect animal

model; to achieve a clearance for spine, the sponsor is expected to provide data from a rabbit posterolateral fusion model. The spine clearance from this pathway is as an autograft extender for posterolateral fusion.

β-TCP is a widely available, FDA-approved material from numerous manufacturers provided in various forms. It is resorbed by osteoclastic activity as a part of bone remodeling as opposed to chemical dissolution.[37] β-TCP with higher porosity and larger pore size ranges will allow for greater cell infiltration and faster resorption.

In posterolateral spine fusion, one β-TCP, Vitoss (Orthovita, Malvern, Pennsylvania) was evaluated in 50 patients as an adjunct to autogenous bone graft. At 5 to 7 months postoperatively, 32 patients were available for follow-up. Of these patients, 100% demonstrated good consolidation of their graft material. The investigator's clinical impression was that Vitoss was facilitating bone formation and reducing the need for ABG harvest.[38] Linowitz and Peppers[39] retrospectively reviewed 7 patients with a 3- to 6-month follow-up who underwent anterior or posterior interbody fusion at 12 levels with an allograft spacer, Vitoss, and venous blood. At follow-up, the investigators reported that solid fusion was achieved in all patients.[39] There are numerous preclinical studies of laboratory-derived β-TCP, but these studies are difficult to interpret for clinical relevance because, as discussed earlier, the material properties greatly dictate the results. There are very few preclinical studies on commercially available β-TCP.

AUTOLOGOUS CELLULAR GRAFTS

Autologous Growth Factors

Platelets isolated from peripheral blood can be an autologous source of growth factors. Forms of autologous growth factors (AGFs) differ by name: platelet-rich plasma, platelet-rich fibrin, platelet gel, etc. However, they are all defined by the volume of the plasma fraction of autologous blood having a platelet concentration above baseline.[40] Platelets are rich in multiple types of biological growth factors, and have the potential to stimulate healing via the recruitment, proliferation, and differentiation of cells involved in tissue regeneration.[41,42] AGFs are created from the patient's own blood, making it a cost-effective alternative to expensive recombinant factors, and eliminating concerns about immunogenic reactions and disease transmission.[38] The bioactive factors released upon platelet activation include platelet-derived growth factor, transforming growth factor, vascular endothelial growth factor, insulin- like growth factor, and epidermal growth factor, among others.[38,43,44] Although the combined actions of all these growth factors and corresponding mechanisms are complex and still poorly understood, there have been promising clinical results for a full spectrum of orthopedic applications.[37,38,45] Among those, the efficacy of AGFs as an osteoinductive material in spinal fusion has been studied.

The results of AGFs in spinal fusion applications are limited and controversial, as there have been conflicting results, and few trials in the literature.[40,46,47] These studies differ in the centrifugation systems, techniques, additives, carriers, platelet concentrations, and experimental protocols. A review article published in 2009 gave autologous platelet concentrates a "grade 2B recommendation," which is defined as a weak recommendation, with alternative approaches likely to be better for some patients, cautioning that the clarity of risk/benefit of platelet gel as an enhancer of the effect of autograft for both posterior lumbar fusion and anterior lumbar interbody fusion is unclear.[48] Additionally, a meta-analysis in 2012 that looked at platelet-rich plasma and evaluated the quality of the literature at the time determined that there was inadequate evidence to definitively conclude that platelet-rich plasma provides a benefit for patients treated with spinal fusion or with respect to healing of the graft.

Bone Marrow Concentrates

Bone marrow aspirate has been recognized as a potential source of MSCs that are readily accessible.[49] Due to this, bone marrow aspirate–derived MSCs are increasingly used in the treatment of a wide variety of orthopedic conditions. The main concern in using simply bone marrow aspirate is that only 0.001% to 0.01% of nucleated cells within bone marrow aspirate are MSCs.[50] To address this issue, various companies have manufactured systems to concentrate the nucleated cell numbers and produce bone marrow aspirate concentrate (BMC). The term *BMC* encompasses all preparations of bone marrow aspirate that have undergone concentration through centrifugation. The exact mechanism of action of BMCs is currently not fully understood. Potentially, the MSCs contained within

BMC provide a direct cell source for repair of the host tissue. Alternatively, the nucleated cells may be capable of delivering various cytokines and growth factors to induce host repair.[51] BMC preparations are now widely used in the treatment of a range of applications. At present, there are over 11 commercially available systems, each yielding unique products, compositions, and characteristics.

The clinical use of BMCs has produced varied and often conflicting results.[52–54] There is a lack of consensus on the optimal preparation, source, delivery, and dosing of BMC preparations. In addition to the characteristics of these different formulations, numerous factors critical to the effect of biologic use, such as the dosage and timing of delivery, remain virtually unexplored. This review systematically presents the available concentration systems and clinical studies in order to provide guidance the potential role of BMCs in spinal fusion surgery.

CLASS III, DRUG-DEVICE COMBINATION PRODUCTS

Bone Morphogenetic Protein

Urist was the first to theorize that osteoinductive activity of DBM was due to active protein molecules. Urist named BMPs that were related to bone healing.[55] Isolating these proteins from bone matrix proved difficult and the first isolated extraction and recombinant form of BMP-2 was described almost 2 decades later, in 1988.[56] To date, although 15 BMPs have been identified and studied, BMP-2 and BMP-7 have been shown to have the most bone forming potential.[57] The recombinant protein available commercially today is a synthetic, genetically engineered version of the natural protein.

As members of the transforming growth factor–β superfamily, BMPs are known to be potent bone-forming agents. They can drive MSCs into the osteoblastic lineage. These proteins alone are considered osteoinductive and are usually added onto a collagen sponge or ceramic carrier. They initiate endochondral bone formation, presumably by stimulating local mesenchymal cells and enhancing bone collagen synthesis.

Preclinical rhBMP-2 Findings

The first question, obviously, is how much of this potent protein should be administered to the site and if this dosage would be site or carrier specific. Sandhu et al. showed in a canine intertransverse spine fusion model that doses of rhBMP-2 on a polylactic acid polymer carrier from 58 to 920 μg were successful in forming fusions at 3 months postoperatively.[58] Using this knowledge, they continued their work in a lumbar interbody fusion in an ovine model. At 6 months postoperatively, they reported all animals appeared radiographically fused. However, histological evaluation revealed something far more telling. Histologically, only 37% of the animals treated with autograft-filled cages had achieved union compared with 100% of the animals treated with rhBMP-2/collagen–filled cages.[58] This exemplifies the value of preclinical work.

Since the ovine model was successful, Boden et al. studied rhBMP-2 on a collagen carrier within a titanium interbody cage in rhesus monkeys.[59] Since dosing was known to be vital but the optimal dose for rhesus monkeys had not been previously established, 2 concentrations of rhBMP-2 (0.75 or 1.50 mg/mL) were tested. The results showed both groups achieved fusion. However, the higher concentration resulted in faster and denser bone formation. This study established the dose used in the IDE trial in the United States.

Although the collagen carrier is the optimal carrier for inside cages in interbody applications, posterolateral spine fusion is a different environment and requires a different carrier. In posterolateral spine fusion, the goal is to bridge bone between the transverse processes. The muscle layer surrounding the graft material is significant and will try to invade the space and cause mechanical compression of the graft material. This can lead to either nonfusion or an hourglass-type fusion that is not as dense in the midregion. Therefore, for these procedures a new carrier had to be identified and dosing concentration again needed to be established for rhBMP-2. Using a ceramic carrier (60% hydroxyapatite and 40% TCP), Boden et al. studied in the nonhuman primate model 3 rhBMP-2 concentrations loaded with a solution containing 0, 6, 9, or 12 mg of rhBMP-2 per side in comparison to a control group, ABG.[59] They reported solid fusions for all 3 concentrations of rhBMP-2 and even fusion in the ceramic carrier–alone group. The ABG group did not achieve fusion in any of the animals. They concluded that the ceramic carrier was a suitable material for posterolateral applica-

tions. This study lead to a clinical trial described below.

Clinical Trials of rhBMP-2

Since the preclinical testing showed efficacy and safety, the multicenter prospective randomized IDE trial was initiated. The study was design for the treatment of degenerative disc disease in the lumbar spine by interbody fusion. Patients were randomized to 1 of 2 groups: rhBMP-2 (1.50 mg/mL) on a collagen sponge with tapered titanium fusion cage (InFUSE/LT-Cage or Medtronic Sofamor-Danek, Memphis, Tennessee) or autograft from the iliac crest with the same tapered titanium fusion cage. In the randomized arm of this trial, 143 patients received the InFUSE/LT-Cage and 136 patients received the LT-Cage with autograft (ABG/LT-Cage). In a continued access arm of the trial, an additional 134 patients received the InFUSE/LT-Cage. The study design was for a 2-year follow-up. The results showed radiographically no difference between the InFUSE/LT-Cage and ABG/LT-Cage groups, each receiving fusion rates above 90% at 2-year follow-up (https://clinicaltrials.gov/ct2/show/results/NCT00485173). The FDA clearance was granted on July 2, 2002, to rhBMP-2 on a type-I collagen sponge in conjunction with a tapered, threaded intervertebral fusion cage (LT-Cage; Medtronic Sofamor Danek, Memphis, Tennessee) for the indication of degenerative disc disease in the lumbar spine.

For the posterolateral spine fusion application, a prospective randomized multicenter clinical study to evaluate with rhBMP-2 on a ceramic carrier (60% hydroxyapatite and 40% TCP) was conducted in 25 patients whose spondylolisthesis did not exceed Grade 1.[60] Patients were randomized to 1 of 3 groups: autograft with pedicle screw instrumentation ($n = 5$) (control), rhBMP-2 with pedicle screw instrumentation ($n = 11$), or rhBMP-2 without internal fixation ($n = 9$). In patients receiving rhBMP-2, the graft material consisted of 20 mg of rhBMP-2 on ceramic granules (10 cm/side). The radiographic fusion rate was 40% (2/5) in the autograft with instrumentation group and 100% (20/20) with rhBMP-2 group with or without internal fixation ($P = .004$). Patient questionnaires revealed a statistically significant improvement in Oswestry scores at 6 weeks in the rhBMP-2–only group and at 3 months in the rhBMP-2–with-instrumentation group. However, the Oswestry scores did not significantly improve in the autograft-with-instrumentation group until 6 months.

On April 30, 2004, InFUSE (rhBMP-2 and collagen sponge) was approved with an intermedullary nail for the treatment of acute, open tibial fractures. In a prospective, multicenter clinical trial, the use of InFUSE with an intermedullary nail was evaluated for the treatment of tibial fractures. Patients all received an intermedullary nail and were randomized to 1 of 3 treatments ($n = 150$ patients): InFUSE at a 0.75-mg/mL concentration, InFUSE at a 1.5-mg/mL concentration, or control (standard of care defined as routine soft-tissue management). The primary endpoint in the study was at 1 year with the primary efficacy evaluated as the proportion of patients requiring secondary intervention because of delayed union or nonunion. At 12 months postoperatively, 421 patients were evaluated. The 1.50-mg/mL rhBMP-2 group had higher union rates, significantly fewer occurrences of secondary interventions, a significantly higher healing rate at the postoperative visits from 10 weeks through 10 months, fewer hardware failures, fewer infections, and faster wound-healing than the control group. The investigators concluded that InFUSE offered significantly superior care to the control.[61]

On March 9, 2011, Medtronic received a nonapprovable letter from the FDA regarding their AMPLIFY rhBMP-2 Matrix. This decision was a result of clinical and safety data from the IDE prospective, randomized, multicenter clinical trial in skeletally mature patients with degenerative disc disease at 1 level from L1 to S1 in 463 patients. Most of the controversy that resulted in the nonapproval stemmed from increased cancer risks in the investigational group in comparison to the ICBG control thought to be linked to the higher dosage than the previously approved version.

In an unprecedented effort, the Yale University Open Data Access project approached Medtronic for funding and access to all of their in-house safety and efficacy data on rhBMP-2. In 2013, 2 publications of the findings of the systematic reviews were published.[62,63] The major finding of the review by Simmonds et al[62] was that rhBMP-2 increased spinal fusion rates at 24 months postoperatively compared with ICBG. They also concluded that evidence of increased cancer incidence was inconclusive. Fu et al[63] reported with respect to

lumbar spine fusion, rhBMP-2 and ICBG were similar in overall success and fusion. For anterior cervical spine fusion, rhBMP-2 was associated with increased risk for wound complications and dysphagia. Their findings differed from those of Simmonds et al[62] regarding the cancer risk. Fu et al[63] found increased risk with rhBMP-2, but event rates were low and cancer was heterogeneous. The discrepancy between the 2 papers is derived from the differences in the studies they included to determine their analyses. Additionally, there have been many recent publications describing retrospective cohort data from centers regarding complications and incidences of cancer after rhBMP-2 usage with mixed findings.[64–67]

Peptide-Based Grafts

Peptide-based bone grafts are a new product category based on biochemistry developed in the early 1990s. The premise of peptide bone grafts is to exploit natural biological activities of MSCs and their osteoblastic lineage cells to initiate the regenerative process of new bone formation. Specifically, peptide bone grafts enhance and accelerate the innate bone-forming biological pathways by stimulating increasing numbers of MSCs in the bony site and stimulating these cells, via cell surface receptor–mediated pathways, to "turn on" the bone-forming molecular cascades. These bone regenerative events accelerate the influx of and activation of MSCs, leading to robust new bone formation.

The most promising of the peptide-based grafts originally identified as candidates for stimulating new bone formation are all "biomimetics" of type I collagen. Type I collagen is the major extracellular matrix component of bone, which for many years was considered to be a passive scaffold in support of the mineralize components of bone. Significant biochemical studies over the last 20 years have demonstrated that, in fact, collagen and other structural proteins provide critical signaling to MSCs and their daughter cells that influence the biological pathways of regenerative events and tissue repair.

To date, approximately 50 individual peptides have been evaluated for their potential role to bind and stimulate MSCs via potential biochemical pathways and the subsequent bone formation cascade. Many of these peptides have shown promise. Of these peptides, from the cell interaction domain of the master control region of type I collagen was found to be 4500 times more potent for cell binding than others. This peptide is a 15–amino acid sequence that represents a unique "kinked" tertiary protein structure on type I collagen that facilitates its presentation to MSCs and is referred to as P-15.

Scaria et al[68] first presented their findings on a synthesized type 1 collagen fragment (P-15) responsible for cellular attachment in mammalian connective tissues in 1989. In 1996, Quan and Bhatnagar published their first investigations on this peptide for application in bone tissues. In this paper, they showed that attaching this 15–amino acid peptide (P-15) to a calcium phosphate anorganic bone mineral (ABM) led to dramatic increases in cellular response in culture, which suggested that this combination might be a useful addition to the bone grafting armamentarium.[69] This in vitro model demonstrated the ABM-bound P-15 stimulated human-derived preosteoblasts to significantly increase the number of bound cells and initiate downstream molecular events associated with differentiation.

Over the subsequent decade, numerous in vitro studies demonstrated that the P-15 peptide would elicit specific biological responses from bone-forming lineage cells (preosteoblasts as well as MSCs). The stimulation and differentiation of MSCs was demonstrated at both the molecular level as seen by upregulation of mRNA production, and the protein level as evidence by the cellular release of bone-regeneration–associated proteins and growth factors, including alkaline phosphatase, BMP-2 and type I collagen.[70] The mechanism of action that elicits these effects is related to the P15 peptide "plugging in" to mmp and $\alpha 2\beta 1$surface receptors on these cells, which turns on the genetically programmed downstream cellular responses.

In vivo studies using a rabbit drill-hole model demonstrated that ABM-bound P-15 significantly enhances the generation of new bone formation yielding histological evidence of mature bone tissue.[71] A sheep interbody lumbar fusion animal study demonstrated that ABM-bound P-15 yielded an equivalent percentage of fusion as the gold standard of ICBG and displayed good trabecular bridging bone structure at 6 months.[72] Finally, rabbit intramuscular implant studies of ABM-bound P-15 established that the P-15 peptide does not support bone formation outside of a bony tissue environment. This can be interpreted as a safety

factor since ectopic bone formation in clinical use is unlikely.

These effects translated from tissue culture into animal implantation, showing promise for bone grafting applications with strong bone formation in the absence of ectopic bone formation.

In 1999, the FDA granted the first of 2 PMAs for the use of the P-15 peptide for dental bone grafting to Ceramed on the basis of a prospective, randomized, level-1 IDE study demonstrating safety and efficacy. This product Pepgen P-15 has been used in approximately 500 000 patients to date in the United States.

In 2000, Cerapedics began developing the P-15 peptide technology platform for use in orthopedics and spine surgery indications called i-FACTOR (P-15 putty). I-FACTOR is a composite bone graft consisting of the synthetic P-15 peptide (biomimetic of the type I collagen peptide) absorbed onto ABM (naturally derived calcium phosphate particles), which are suspended in an inert hydrogel carrier. Cerapedics received the first CE mark for their i-FACTOR product in 2008 for all orthopedic applications including spine. Under the CE mark, the product has been used in $>$ 50 000 patients to date.

Cerapedics initiated an IDE trial for single-level ACDF in an allograft ring in 2006, which culminated in PMA in 2015. This FDA-approved trial was prospective, randomized, blinded, controlled, and statistically powered, and thus represents level 1 study data.[73] In this 319-patient trial, i-FACTOR successfully met the predefined noninferiority criteria for radiologic fusion (88.9% versus 85.8% for control), neck disability index (28.8% change versus 27.4% for control), neurological success (93.7% versus 93% for control), and safety (97.5% versus 95.4% for control.) More importantly, a FDA-mandated, prospectively designed statistical analysis of the overall clinical success, defined in the as individual patients who were successful for all 4 of the primary outcomes, demonstrated statistical superiority to local autograft in overall clinical success (68.8% versus 56.9%) at 12 months. The statistical superiority was maintained at the 24-month evaluation.

Following the introduction of the i-FACTOR bone graft in the European Union, based on a CE mark, numerous clinical evaluations were performed with i-FACTOR in the lumbar clinical indication. Mobbs et al. published a prospective anterior interbody fusion study in which i-FACTOR was used as a stand-alone bone graft inside a PEEK interbody device.[74] In this study, an independent radiological evaluation found a 94% fusion rate by thin-cut computed tomography at 24 months along with a statistical improvement in all clinical evaluations. This study represents an approved use in the European Union and Australia, which would be considered an off-label use in the United States.

Lauweryns et al. published the results from a prospective intrapatient randomized study comparing i-FACTOR to local autograft in posterior interbody fusions.[75] In this study, contralateral cages were randomized to be filled with either i-FACTOR or local autograft, and fusions were assessed by thin-cut computed tomography. The results demonstrated that i-FACTOR was statistically superior regarding percentage of patients with complete bridging fusion at both 6 months (97.7% for i-FACTOR versus 59.1% for autograft) and 12 months (97.8% for i-FACTOR versus 82.2% for autograft). At 24 months, the fusion rates were no longer statistically different. This study represents an approved use in the European Union and Australia and would be considered off label in the United States.

Both the well-established mechanism of action regarding the stimulatory effects of P-15 peptide and the extensive clinical data resulting from an IDE level 1 clinical study strongly support the safety and efficacy of P-15 peptide in the form of i-FACTOR.

CODING

Bone Grafts in Spine Surgery

There are several category I Current Procedures Technology (CPT) codes to report the various types of bone grafts used in spine surgery. These are add-on codes and should be reported in addition to the primary procedure.

+ ***20930*** - *Allograft, moralized, or placement of osteopromotive material, for spine surgery only (List separately in addition to code for primary procedure.)*

+ ***20931*** - *Allograft, structural, for spine surgery only (List separately in addition to code for primary procedure.)*

+ ***20936*** - *Autograft for spine surgery only (includes harvesting the graft); local (eg, ribs, spinous process, or laminar fragments) obtained from same incision (List separately in addition to code for primary procedure.)*

+ ***20937*** - *Autograft for spine surgery only (includes harvesting the graft); morselized (through separate skin or fascial incision) (List separately in addition to code for primary procedure.)*

+ ***20938*** - *Autograft for spine surgery only (includes harvesting the graft); structural, bicortical or tricortical (through separate skin or fascial incision) (List separately in addition to code for primary procedure.)*

Note: do not append modifier 62 to these codes.

Also note, these codes should only be reported in conjunction with 22319, 22532, 22533, 22548-22558, 22590-22612, 22630, 22633, 22634, 22800-22812.

Bone Marrow Aspiration for Bone Grafting in Spine Surgery

Effective January 1, 2018, CPT code 38220 should only be used to report bone marrow aspirations performed for *diagnostic* purposes and should no longer be used to report bone marrow aspiration for bone grafting in spine surgery. There is now a category I code specifically to report bone marrow aspiration for bone grafting in spine surgery, CPT code 20939. This is an add-on code and should be reported in addition to the primary procedure.

+ ***20939*** - *Bone marrow aspiration for bone grafting, spine surgery only, through separate skin or fascial incision (List separately in addition to code for primary procedure.)*

Note: use modifier 50 with this code for bilateral procedures.

Also note, this code should only be reported in conjunction with 22319, 22532, 22533, 22534, 22548, 22551, 22552, 22554, 22556, 22558, 22590, 22595, 22600, 22610, 22612, 22630, 22633, 22634, 22800, 22802, 22804, 22808, 22810, and 22812.

Bone Marrow Aspiration for Platelet-Rich Plasma Injection

Currently, bone marrow aspiration for platelet-rich stem cell injections should only be reported using category III code, 0232T.

0232T - *Injection(s), platelet-rich plasma, any site, including image guidance, harvesting and preparation when performed*

CONCLUSION

Bone grafting is an essential part of spinal surgery and an ever-evolving science. With each new advance, one needs to understand the characteristics of the material, its mechanism of action, the regulatory pathway by which it came to market, and the preclinical and human clinical evidence available on which to base a clinical use decision.

Nonstructural cancellous allograft remains a viable and inexpensive option that is supported with reasonable (but not level I) clinical data as an autograft supplement or alone in low-demand clinical applications, such as adolescent scoliosis.

The DBMs and synthetic bone substitutes are FDA cleared via the 510(k) process on the basis of animal data for use as autograft extenders in posterolateral fusion. At the time of this writing, there have been 398 products 510(k) cleared under product code MQV (filler, bone void, calcium compound.) There are a few published clinical studies on several of these products, including some level I studies, which support their use as autograft extenders.

Cellular allograft materials currently being marketed under the FDA's HCT/P guidance do not yet have compelling clinical evidence to support their broad use. The questions regarding the suitability of their classification under HCT/P is likely to continue to be debated in the coming years.

The basic science is compelling, and there is some quality suggestive clinical evidence supporting the use of appropriately aspirated bone marrow aspirate as an adjunct to bone grafting in spinal fusion. The various medical devices available for concentrating this valuable source of autologous stem cells seem promising, but the supportive evidence base is still being developed. The use of concentrated platelets to enhance bone formation at this point is still developing with emphasis on how the platelets are obtained.

At the current time there are 2 drug-device combination products approved via the PMA process for spinal use by the FDA based on level I clinical trials showing them to be safe and effective as autograft replacements. These 2 spine products are InFuse (rhBMP-2), and i-FACTOR (P-15 peptide). Additionally, the drug-device combination product Augment (rh platelet-derived growth factor) has been PMA approved for ankle and hindfoot arthrodesis.

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