of chondrogenic factors. Other products in Regentis’ pipeline include GelrinBone for use in craniomaxillofacial defects, bone voids caused by surgical interventions, long bone defects and fracture healing (non-weight bearing); and GelrinSpine, a matrix enhanced with TGF-beta for non-injurious bone formation and spinal fusion. The product may be placed in the fusion site using preformed constructs or by injection.

Replication Medical received funding from Abbott Spine which will help expand development of Replication’s hydrogels and implants for spine care. The company’s minimally invasive NeuDisc is a hydrogel-based spinal nucleus implant (based on Aquacryl proprietary polymer) that is inserted in a dehydrated, rolled-up wafer. When hydrated, the device locks in place, replacing the natural nucleus.

SaluMedica’s lead technology is Salubria, a biostable, biomimetic hydrogel material that contains water in similar proportions to human tissue. Salubria has been shown to allow new cells to grow on it. The company received Canadian regulatory clearance and CE Mark approval for its SaluCartilage implant line, indicated for use in treatment of painful chondral or osteochondral defects of the articular cartilage surface. Arthrex distributes SaluCartilage on a limited basis in Europe, and in 2005 SaluMedica engaged in contract negotiations with reps in more than 20 countries to establish a network of independent distributors.

SBM specializes in resorbable surgical devices based on synthetic materials. The company’s Bio1 implant, made from Biosorb synthetic β-tricalcium phosphate, is FDA cleared for bone void filling and was reportedly the first such product approved in Europe under the CE Mark. SBM’s materials, including Biosorb, Synatite (synthetic nonresorbable hydroxyapatite) and Duosorb (tricalcium phosphate ceramic and Poly DL lactic acid), form the basis for products such as the Tecma System for cervical interbody arthrodesis (Bio-Tecma resorbable and Tecma-Fx nonresorbable implants), the Otis Systems for high tibial osteotomy by internal addition, and Ligafix bioactive interference screws. All products are approved under the CE Mark.

Scient’x entered the bone graft substitute market with the U.S. launch of DyNoss, a cancellous bone void filler manufactured from a proprietary combination of HA/β-TCP.
Scil Biomedicals’ expertise lies in tissue regeneration using a combination of recombinant proteins or peptides and a variety of biomaterials. Scil and Biopharm have developed MD05 for bone augmentation. MD05 brings together a bone growth-inducing protein rhGDF-5 coated onto a β-TCP carrier, with the company claiming that the product is the first calcium phosphate-based osteoinductive bone regeneration material developed for maxillofacial indications.

Products in research at Scil include ST01/ST02, calcium phosphate based osteoinductive bone regeneration materials for spinal fusion applications. A proof-of-concept study for ST01 revealed superior efficacy of the material to autologous bone in an in vivo preclinical study for posterolateral interbody spinal fusion. Scil has also performed preclinical efficacy testing of its ST03 product in animal models. ST03 consists of a chondrogenic protein, coated onto or incorporated into a biocompatible, biodegradable matrix. The material will likely have application in the treatment of osteochondral defects.

Skeletal Kinetics focuses on fracture repair and “mechanobiologic” solutions in bone repair. Its family of products includes resorbable Callos bone void filler (calcium phosphate-based) and a Callos formulation for craniomaxillofacial applications; Impact, a moldable, impactable material that may have application in augmenting fixation; Inject, an injectable paste; and OsteoVation CMF bone void filler, which may be used in the restoration or augmentation of bony contours of the craniofacial skeleton. All are FDA-cleared, and Callos is CE Marked. Skeletal Kinetics distributes Callos in the U.S. through a combined direct sales force, independent sales agents and distributors. Callos is also distributed internationally in certain countries in Europe and Asia-Pacific through a network of independent distributors. In the U.S., OsteoMed distributes OsteoVation as a private label product.

Smith & Nephew has retained non-exclusive rights to NeoCyte, a tissue-engineered cartilage currently in clinicals in the U.S. for ACL repair. In other orthobiologic initiatives, Smith & Nephew markets Jax, a calcium sulfate bone graft substitute material that may also have application as a carrier for pharmaceuticals used in treating bone infections, and also Viagraft DBM in five formulations: crunch, flex sheets, gel, paste and putty. The company’s agreement with Osteotech also provides it with DBM products, as well.
Smith & Nephew is investigating the use of mesenchymal stem cells in the repair of bone, cartilage and ligaments. Products resulting from research are reportedly five to ten years from being available to patients if the company decides to invest substantially into development of the technology.

**Stryker Biotech**’s OP-1 Implant, a human recombinant osteogenic protein, has been cleared for marketing in Australia and Canada for treatment of nonunion fractures of long bone; in Europe for nonunion fractures of the tibia; and in the U.S. under a Humanitarian Device Exemption for use as an alternative to autograft in certain recalcitrant long bone nonunions and in revision spine surgery. Stryker completed enrollment in a Japanese pivotal trial of OP-1 in non-cage, non-instrumented posterior lateral spine fusion and plans to combine OP-1 with its Ray TFC fusion cage. The company is also conducting a multicenter pivotal trial in the U.S. and Canada for posterolateral spine fusion using OP-1 Putty to treat degenerative spondylolisthesis, and anticipates that the evaluation of the 297 enrolled patients will be completed in late 2005.

Stryker also markets BoneSource, a calcium phosphate-based bone void filler cleared for CMF applications for years in the U.S. In 2003, Stryker received FDA clearance for BoneSource in orthopaedic applications (e.g. for bony voids not intrinsic to the stability of the bony structure) in extremities, spine, and pelvis.

Stryker is teamed with TEI Biosciences in an agreement that gives Stryker rights to the exclusive supply and distribution of TEI’s TissueMend Soft Tissue Repair Matrix, which was cleared by FDA as a general surgical mesh for the repair and reinforcement of soft tissues where weakness exists. TissueMend has application for the repair of disorders of the joints and supporting tendinous, ligamentous and capsular supporting structures (excluding conditions related to spinal pathologies).

Synthes markets numerous structural and base allograft products through its distribution agreement with Musculoskeletal Transplant Foundation, along with XR calcium phosphate powder; ChronOs TCP wedges, blocks, cylinders and granules; and SRS and CRS, injectable carbonated apatite bone cements. SRS is cleared for broad orthopaedic applications outside the U.S., while its use in the U.S. is limited to

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adjunctive or augmented treatment for unstable distal radius fractures and for bone void filling in extremities, spine and pelvis.

Teknimed markets a variety of HA and TCP synthetic bone graft substitutes including Ceraform 400 and Ceraform 200 (granules and blocks), Cementek LV (powder and injectable) and Tri HA+ in block form. All are cleared for use in the U.S. and Europe for orthopaedic applications.

Aside from TissueMend, TEI’s orthobiologic platform consists of a remodelable collagen fiber scaffold enriched with a proprietary growth factor for use in spinal fusions and approaches for the rebuilding and repair of discs. The company’s collaboration with Medtronic Sofamor Danek may lead to commercialization of spinal products. TEI has also generated ligament, tendon and cartilage prototypes and an injectable bone precursor cement with tissue specific signaling complexes.

Tepha’s patented technologies center on the use of genetic engineering to create naturally-synthesized biopolymers (e.g. polyhydroxyalkanoate copolymer) that the company can process with a variety of mechanical properties. Tepha will develop resorbable polymers for use in such orthopaedic products as internal fixation devices, articular cartilage and meniscus regeneration devices, ligament and tendon grafts, spinal cages and bone graft substitutes.

The CryoSeal FS System from ThermoGenesis is used to prepare autologous hemostatic and adhesive surgical sealants from patient blood in approximately an hour. The company entered into an agreement with Affinity Supplies for distribution of the CryoSeal Fibrin Sealant System and Thrombin Processing Device (TPD) in Ireland, for use in orthopaedic and other specialties. ThermoGenesis expects product distribution in a majority of European countries before the end of 2005.

ThermoGenesis commenced shipments of its TPD to Biomet’s Cell Factor Technologies subsidiary. The disposable kit, which produces stable, activated thrombin from a patient’s blood in under 30 minutes, will enable Cell Factor to serve orthopaedic, spinal and maxillofacial applications in Europe, Canada and Asia.
Through expertise in signaling pathways that govern the recruitment, proliferation and differentiation of musculoskeletal cells, TiGenix develops cell-based tissue-engineered products for treatment of joint surface and bone defects. The company’s first product is ChondroCelect, an autologous chondrocyte implant (ACI) that incorporates the company’s proprietary genetic marker technology to improve the selection, characterization and expansion of cartilage-forming cell populations. TiGenix has been able to consistently grow hyaline cartilage \textit{in vivo} and plans to leverage the technology to other orthopaedic applications. TiGenix is conducting a randomized, multi-national Phase III clinical trial comparing ChondroCelect to microfracture, the current standard of care, in the repair of symptomatic knee cartilage defects. Twelve hospitals will participate in the trial, in which 118 patients have already been enrolled. Results are expected in 2006. Further, the company filed an Investigational New Drug application for the product for the structural and functional repair of knee cartilage defects.

In the pipeline at TiGenix are ChondroCelect-P (which uses adult stem cell technology); technologies to treat osteochondral defects; and cell seeded bone matrices for the repair of large bone defects. Biomet’s subsidiary, IQL, distributes the ChondroCelect ACI procedure in Spain and Portugal.

Tigenix signed a collaborative agreement with ProStrakan to research and develop new treatments for osteoarthritis and cartilage repair.

\textbf{Tissue Genesis}, in collaboration with the \textbf{University of Michigan}, seeks to develop 3D tensile connective tissues (e.g. tendons and ligaments) for replacement therapy. The company reportedly has already engineered self-organizing connective tissues without the use of artificial scaffolds, allowing cells within the tissue to generate their own extracellular matrix better suited to the eventual requirements of the tissue when implanted into the joint. Tissue Genesis uses a “Bio-Optimization System,” an automated cell and tissue culture technology whose architecture reportedly provides a physiologic support system to ensure optimal conditions for cell growth and maintenance. Tissues would be “trained” in this system prior to their implantation.

\textbf{Tissue Regeneration} started operations to capitalize on the development of human tissue replacements for damaged or diseased soft tissue. The company’s first product is a silk-based device and ACL tissue
engineering methodology, which entails seeding a silk-fiber mold with donor progenitor stem cells, incubating them and reimplanting them. Through a grant from the National Institutes of Standards and Technology, Tissue Regeneration will apply what it is learning about the ACL to the rotator cuff tendon in the shoulder and non-loading and loading bone grafts. The company expects to initiate ACL and rotator cuff trials in humans by the end of 2006.

Tredegar sold or assigned substantially all assets of its orthobiologics company to Therics, LLC. Therics has clearance in the U.S. to market a range of β-TCP bone graft products, all of which are manufactured using the company’s novel TheriForm microfabrication process, which the company licensed from the Massachusetts Institute of Technology. Through the proprietary TheriForm technology, Therics is able to create precise three-dimensional (3D) geometries and architectures with controlled porosity and ingrowth channels. TheriForm machines can place synthetics, allograft or growth factors at specific geometric locations within the implant, and in gradients, to foster optimal bone ingrowth.

Products available from Therics include TheriFil, TheriRidge Block, TheriLok, TheriLink, TheriWedge and TheriMatrix, along with DBM and base allograft tissue.

Tutogen earned accreditation from the American Association of Tissue Banks. The company processes, develops, manufactures and markets allograft and bovine implants used in bone and soft tissue repair. Zimmer Spine distributes the company’s line of structural and non-structural Puros Allografts for spinal indications. Tutogen also distributes Ligatech sports medicine allografts (bone-tendon-bone implants) through another network in the U.S. The company expects to shift its focus toward expanding its dental revenue and establishing business that is not as reliant on Zimmer, which owns a 30 percent stake in Tutogen. Further, in Italy, the company has partnered with new distributors and is seeking tissue bank approval status.

Researchers from the University of British Columbia and Vancouver Coastal Health Research Institute are developing a “living glue” which they hope might render revisions and other joint repairs obsolete within ten to 15 years. The glue combines growth factors, calcium, phosphate and stem cells from a patient’s own bone marrow to promote bone regeneration and thus, better secure artificial joints. The
team will focus first on applications in revision hip surgery, and hopes to complete animal testing in four to five years. Future uses could include osteoporosis treatment and bone defect repair.

Vertebron’s relationships with Musculoskeletal Transplant Foundation and U.S. Tissue & Cell provide the company with demineralized matrix devices and structural allografts in proprietary designs for spinal fusion applications, such as the PLF (posterolateral fusion) Allograft System.

Wright Medical Group markets a wide variety of bone graft substitute materials including OsteoSet, Allomatrix, MIIG (Minimally Invasive Injectable Graft), Ignite ICS (Injectable Cellular Scaffold), Graft-Jacket and CellPlex.

OsteoSet is a proprietary resorbable surgical grade calcium sulfate substitute used primarily in filling non-load bearing voids in long bones, spine, pelvis and extremities. Wright has developed an OsteoSet with DBM as well. The company’s Allomatrix line (DBM+OsteoSet) includes an injectable putty, an injectable putty with cancellous bone granules (Allomatrix C); a custom bone graft putty; and Allomatrix DR Graft, optimized for application in smaller fractures due to its smaller particle size of cancellous bone granules. The MIIG family includes an injectable form of the company’s calcium sulfate paste that hardens in the body, as well as a high-strength injectable calcium sulfate/calcium phosphate composite intended for use in treatment of distal radius, tibial plateau, pilon and certain spinal fractures. Wright’s IGNITE ICS combines calcium sulfate, DBM and autologous bone marrow aspirate for the treatment of problem fractures and delayed nonunions, while CellPlex TCP Graft features a TCP cancellous scaffold for cell infiltration. CellPlex granules are packaged within the Infiltrate Marrow Infusion Chamber, which allows for minimally invasive aspiration and infusion of the patient’s own bone marrow into the CellPlex matrix. To date, Wright is the only company to have received FDA clearance to market all of its allograft bone void fillers in the U.S.

Finally, Wright markets GraftJacket products through its relationship with LifeCell. The GraftJacket line includes Periosteum Replacement Scaffold for use as an onlay periosteal replacement scaffold for uncontained bone defects, a regenerative tissue matrix for hand surgery applications, tendon and ligament repair scaffolds and the Rotator Cuff Tendon Reinforcement Scaffold. The GraftJacket technology incorporates
biological substrate components (e.g. collagen, elastin, chondroitin sulfate, hyaluronic acid, fibroblast growth factor, etc.), which are processed to preserve the biochemical matrix and create an intact extracellular framework. The end result is a scaffold that allows for revascularization and cellular repopulation.

**Xylos** has developed a technology platform based on biosynthesized cellulose, a non-woven, multi-layered, 3D structure whose performance can be engineered for specific applications. Products being researched by Xylos include those for musculoskeletal repair. The company has developed and tested prototypes for rotator cuff repair.

Zimmer initiated the U.S. launch of the Zimmer Collagen Repair Patch, a chemically crosslinked, acellular sheet of collagen/elastin processed from porcine dermis and FDA-cleared for use in rotator cuff repair. The underlying technology originates from **Tissue Science Laboratories**, which markets the product as Permacol for non-ortho applications.

Zimmer acquired from **Re vivicor** the worldwide exclusive distribution rights for genetically-engineered xenogeneic tissues for regenerative therapies. Zimmer will initially develop the technology for applications such as tendon, ligament, meniscus, cartilage, bone and spinal nucleus repair and replacement.

Zimmer is involved in distribution relationships with NeuColl and Tutogen. The company will also work with two universities to investigate gene therapy in the treatment of articular cartilage and meniscal damage.

Other companies with bone graft substitute materials on the market include **Asahi**, R and D Medical (Formagraft Collagen Bone Graft Matrix), **Taisho** and **Mitsubishi Pharma** (Biopex), **Toshiba Ceramics**, etc. Of note, many Japanese ceramics companies have diversified outside of semiconductors (their key strengths) into biologics, as evidenced by Toshiba Ceramics’ approval to market its Neobone porous HA artificial bone filler.
Other companies with ACI technologies on the market outside the U.S. include CellCoTec (4CRT), CellTec (ChondroTec), Interface (Cartilink) and Karocell in Europe; Cellontech in Korea (Chondron), J-TEC in Japan, and ProChon (BioCart-II) in Israel.

Viscoelastics – Adhesion Prevention and OA Pain Relief

Among viscoelastics, hyaluronic acid (hyaluronan) plays the most prominent role in orthopaedics. A naturally occurring biopolymer, hyaluronic acid is found naturally in connective tissue, with its greatest concentrations in, among other places, the synovial fluid of articular joints. Its use, therefore, centers primarily on injection into the intra-articular space for relief of OA and restoration of joint fluid. Other viscoelastic products have found application in the prevention of post-surgical adhesions and failed back surgery syndrome.

Anika Therapeutics manufactures Orthovisc, an ultra-pure, medical grade, high molecular weight hyaluronic acid extracted from rooster and hen combs and used to treat pain caused by OA of the knee. Orthovisc treatment involves a series of three intra-articular injections one week apart. DePuy Mitek and sister company, Ortho Biotech, distribute Orthovisc in the U.S. and Mexico for treatment of knee OA pain, with Mitek targeting arthroscopists and orthopaedic surgeons and Ortho Biotech focusing on serving rheumatologists and other specialists. Rivex represents Anika in Canada, while a variety of distribution groups handle the product’s sales and marketing in other areas outside the U.S. and Canada.

Anika also has developed the Incert family of chemically modified, cross-linked forms of hyaluronic acid for use in preventing surgical adhesions. The company initiated a human pilot clinical trial in the U.K. in early 2004 for Insert-S for the prevention of adhesions following spinal surgery. At the end of 2004, approximately two-thirds of the targeted 45 patients had been enrolled in the study and Anika had received CE Mark approval for the product. Pending results from the trial, Anika may initiate a pivotal PMA in the U.S.

Using bacterial fermentation, Hyaltech produces Fermathron, an injectable (five weekly injections) hyaluronan-based formulation for treatment of knee OA. Biomet distributes the CE Mark-approved product in most of Europe, with Celltech handling distribution in Germany.