TABLE E-1 Literature Search Terms*

1	Gene therapy
2	Tissue engineering and cell-based therapies
3	Parathyroid hormone as a bone stimulator
4	Use of physical forces in bone-healing
	a. Electromagnetic field/pulsed electrical field
	b. Extracorporeal shock wave
	c. Ultrasound
5	Bone-graft substitutes
	a. Osteoconductive materials
	1. Calcium sulfate
	Trade names: Osteoset (Wright Medical Technology, Arlington, Tennessee) and BonePlast (Interpore Cross International, Irvine, California)
	2. Calcium phosphate (ceramics)
	Hydroxyapatite
	Tricalcium phosphate
	3. Coralline hydroxyapatite (interporous hydroxyapatite)
	Trade names: Biocoral (Inoteb, Saint Gonnery, France), Pro-osteon 200R and 500R (Interpore Cross International)
	4. Tricalcium phosphate
	Trade names: Norian skeletal repair system (SRS; Norian Corporation, Cupertino, California), Vitoss (Orthovita, Malvern, Pennsylvania), Biobon (Biomet Merck Biomaterials, Darmstadt, Germany)
	5. Type-I collagen
	Trade names: Collagraft (Zimmer, Warsaw, Indiana), Healos/MP-52 (BMP family) (Orquest, Mountain View, California)
	6. Nonbiological substances
	Degradable polymers
	Bioactive glasses
	Metals (sintered cobalt chromium beads, titanium alloy fiber metals, plasma-sprayed surfaces, tantalum)
	Trade name: Immix (Osteobiologics, San Antonio, Texas)
	b. Osteoinductive materials and peptide-signaling growth factors
	1. Growth factors–TGF, PDGF, autologous growth factors, bovine-derived BMP extract (NeOsteo; Intermedics Orthopedics, Denver, Colorado), bFGF, Ossigel (Orquest) (bFGF and hyaluronic acid), BMP-rhOP-1, rhBMP-2, rhBMP-7
	2. Demineralized bone matrix
	3. Bone-marrow aspirate

*bFGF = basic fibroblast growth factor; BMP = bone morphogenetic protein; OP = osteogenic protein; PDGF = platelet-derived growth factor; TGF = transforming growth factor.

TABLE E-2 Level-I Studies on the Use of Physical Forces in Bone-Healing and Repair*

Modality	Author(s) (Year)	Number of Subjects	Location	Result†	Complications, Time to Union	Conclusions
Electrical/electromagnetic field	Aaron et al.[14] (2004) meta-analysis	N1 = 1718 N2 = 569	Tibial nonunion N1 = PEMF N2 = Surgical	N1 = 81% N2 = 82%		
	Simonis et al.[15] (2003)	34 N1 = 18 N2 = 16 (placebo)	Tibial nonunion—cast treatment	N1 = 16 (89%) N2 = 8/16 (50%)	6 mo	Significant. Smokers—control not matched
	Brighton et al.[16] (1995)	271 N1 = 167 N2 = 56 N3 = 48	Tibial nonunions N1 = direct current N2 = CCES N3 = Bone graft	Identified seven risk factors in the group		No statistical difference among treatment groups when no risk factor is present. Poor results for atrophic nonunions
	Sharrard[17] (1990)	45 N1 = 20 N2 = 25 (placebo)	Tibial nonunion—cast treatment	N1 = 10 union (50%) N2 = 3 union (12%)	12 wk	Very significant difference. Age not matched
Low-intensity ultrasound therapy	Heckman et al.[49] (1994)	67 N1 = 33 N2 = 34 (placebo)	Closed/grade-1 open tibial fractures—cast treatment	N1 = 86 days to union N2 = 114 days to union	24% reduction in clinical healing time; no complications	38% decrease in overall time to healing
	Emami et al.[50] (1999)	32 N1 = 15 N2 = 17 (placebo)	Tibial fractures—intramedullary nail	N1 = 113 days to union N2 = 112 days to union	No difference	No beneficial effect
	Busse et al.[47] (2002) meta-analysis	158	Long bones—tibial nonunions	Faster healing	None	Faster healing by 64 days; no benefit with prior reaming
	Kristiansen et al.[51] (1997)	61	Dorsally angulated distal radial fracture	Time to union 38% shorter	None	Accelerated healing

*N1, N2, N3 = group 1, group 2, group 3, respectively. †Unless otherwise noted, percentages in this column refer to the percent of patients with successful union. CCES = capacitive coupled electrical stimulation; PEMF = pulsed electromagnetic fields.

TABLE E-3 Level-I Studies on the Use of Biological Forces in Bone Healing and Repair*

Modality	Author(s) (Year)	Number of Subjects	Location	Result	Time to Union; Complications	Conclusions
Coralline hydroxyapatite (CoHA)	Shors[57] (2003)	167 (174 defects)	Resorbable CoHA (Pro-Osteon 500) vs. autograft for repair of long-bone defects	CoHA: time to union not significantly different (mean 4.5 mo); 55% osteointegration index	Time to union not significantly different than controls (mean time to union for CoHA group = 4.5 months); 55% osteointegration index for CoHA group	Acceptable bone graft substitution of long-bone defects
	Bucholz et al.[62] (1989)	40	CoHA implants vs. autograft for split-depression tibial plateau fractures	No significant difference in clinical results; no bioresorption of CoHA	None	CoHA implants compare favorably to autograft
Tricalcium phosphate (bone cement)	Mattsson and Larsson[63] (2006)	118; N1 = 60 controls; N2 = 58	Displaced femoral neck fractures; augmentation after internal fixation; N1 = closed reduction and two cannulated screws; N2 = screws + $CaPO_4$ cement	No difference in pain or muscle strength; 34 (N1 = 14, N2 = 20) conversions to total hip arthroplasty secondary to loss of reduction, nonunion, or osteonecrosis	No difference in pain of muscle strength between groups; 34 total conversions to total hip arthroplasty secondary to loss of reduction, nonunion, or osteonecrosis (14 in tricalcium group; 20 in control group)	$CaPO_4$ cement augmentation not recommended secondary to high rate of revision to total hip arthroplasty

	Mattsson et al.[64] (2005)	112; N1 = 57; N2 = 55	Unstable trochanteric fractures; N1 = sliding screw alone; N2 = sliding screw device + $CaPO_4$ cement (Norian SRS) for internal fixation	N2 lower pain scores, better return to activities of daily living, improved Short Form-36 score at 6 wks/mo postop	6 wk/mo	Improved quality of life during healing
	Mattsson and Larsson[65] (2004)	26; N1 = 11; N2 = 10	Unstable intertrochanteric fractures; N1 = sliding screw device augmented with $CaPO_4$ cement; N2 (control) = sliding screw device alone	Less movement and decreased varus angulation compared with control	1 wk/6 wk/6 mo	Effective
	Mattsson and Larsson[66] (2003)	40	Displaced femoral neck fractures; cannulated screws vs cannulated screws + $CaPO_4$ cement augmentation	Less varus angulation and distal migration	1 wk/6 wk	Favorable

	Cassidy et al.[67] (2003)	323	Distal radial fractures; closed reduction and immobilization with and without Norian SRS cement	Norian SRS group: better grip strength, range of motion, digital motion, hand use; less swelling; lower infection rate	24 mo; Four patients with intra-articular cement extravasation; Extraosseous cement in 112 patients (35%); loss of reduction highest with this subgroup	Recommended
	Zimmermann et al.[68] (2003)	52 (menopausal, osteoporotic females)	Unstable intra-articular distal radial fractures; Percutaneous pinning + casting for 6 wk (control) vs. Norian SRS + pinning + casting for 3 wk	Norian SRS group: better functional outcome, restoration of movement and grip strength ($p < 0.001$); Control group: higher loss of reduction rate ($p < 0.001$)	2 yr (range, 21-29 mo)	Effective

	Sanchez-Sotelo et al.[69] (2000)	110; N1 = 55; N2 = 55	Old distal radial fractures; N1 = closed reduction, stabilization by Norian SRS, and casting for 2 wk; N2 = closed reduction and a cast for 6 wk	N1: 81.54% satisfactory results at 1 yr, less pain, earlier restoration of movement and grip strength	6 and 12 mo; N1: 38 soft-tissue cement extrusions, 10 malunions, 2 median nerve compressions, 3 reflex sympathetic dystrophy, 2 extensor pollicis longus ruptures, 1 refracture, 1 intra-articular SRS deposit	Recommended
Collagen type-I	Chapman et al.[70] (1997)	213 (249 fractures); N1 = 117 (control); N2 = 132	Long-bone fractures; N1 = autogenous iliac bone graft (IBG); N2 = collagen-calcium phosphate ceramic graft (Collagraft)	No significant difference in rates of union, functional outcomes, prevalence of complications (except for infections greater in IBG group)	24 mo; N2: 9 infections, 2 refractures, 12 patients with positive antibody titers to bovine collagen (no associated complications with fracture-healing); IBG group: 22 infections, 5 refractures	Safe and effective

	Cornell et al.[71] (1991)	267; N1 = 128; N2 = 139	Acute long-bone fractures; N1 (control) = cancellous autograft; N2 = Collagraft	No significant difference in: hospital length of stay, pain scores, functional outcomes, radiologic union; Collagraft group had shorter operative time	6 wk–24 mo; N1 = 13 fracture-site infections, 6% fracture-healing complication rate, 13.3% wound-healing complication rate; N2 = 9 fracture-site infections, 8.1% fracture-healing complication rate, 12 wound-healing complications	As effective as autogenous bone graft
Bone morphogenetic proteins	Friedlaender et al.[88] (2001)	124	BMP-7; tibial nonunion; N1 = 61 nail + bone graft only; N2 = 63 nail + rhBMP-7 in collagen carrier	N1 = 81% union in nail + bone graft group; N2 = 85% union in nail+ BMP group	No statistical difference; no donor-site morbidity in BMP group; 9-mo follow-up	Results as good as autograft

	Govender et al.[89] (2002)	450 (421 follow-up)	Open tibial fracture; N1 = nailing only; N2 = nailing + rhBMP-2	rhBMP-2 had 44% less risk of failure due to delayed union	94% at 12-mo follow-up; Fewer hardware failures, fewer infections, and faster wound-healing (83% fracture-healing at 6 wk compared with 65%)	Significant results
	Swiontkowski et al.[90] (2006) subgroup analysis	510	Open tibial fracture—rhBMP-2; Nail + BMP in 113 and only nail in 113. Randomized	Better results	Fewer bone grafts, surgeries; lower infection; higher union rates	Recommend absorbable collagen sponge implant
	Giannoudis and Tzioupis[91] (2005)	653	BMP-7; long-bone nonunions, periprosthetic fractures, joint arthrodesis, acetabular reconstruction, distraction osteogenesis	82% success (535/653)	No complications	Highly recommend
	Zimmermann et al.[92] (2006)	23	Long-bone nonunion; N1 = 10 BMP-7 + osteosynthesis + bone graft; N2 = 5 BMP-7 + bone graft; N3 = 7 only BMP-7	95.6% (22/23)	Minimum 6 mo; no complications	Additional innovative therapy

	Bilic et al.[93] (2006)	17	Scaphoid nonunion—proximal pole	N1 = 6 autograft; N2 = 6 autograft + OP-1; N3 = 5 allograft	24-mo follow-up; OP-1 reduced healing time by 4 wk	OP-1 improved the performance of both autologous and allogeneic bone implants and reduced healing time to 4 wk compared with 9 wk in group 1
	Jones et al.[94] (2006)	30	Tibial fractures with bone gap (mean = 4 cm); N1 = 15 autograft; N2 = 15 allograft + rhBMP-2	N1 = 10 union (66.6%); N2 = 13 union (86.66%)	No complications	Safe and as effective as autogenous bone graft

*N1, N2, N3 = group 1, group 2, group 3, respectively. BMP = bone morphogenetic protein; $CaPO_4$ = calcium phosphate; Op = osteogenic protein; ; rhBMp = recombinant human BMP; SRS = Skeletal Repair System; THA = total hip arthroplasty.