US00RE42208E

(19) **United States**

(12) **Reissued Patent**

Truncale et al.

(10) **Patent Number: US RE42,208 E**

(45) **Date of Reissued Patent: Mar. 8, 2011**

(54) **GLUE FOR CARTILAGE REPAIR**

(75) Inventors: **Katherine Gomes Truncale**, Hillsborough, NJ (US); **Arthur A. Gertzman**, Flemington, NJ (US); **Moon Hae Sunwoo**, Old Tappan, NJ (US); **William W. Tomford**, Belmont, MA (US)

(73) Assignee: **Musculoskeletal Transplant Foundation**, Edison, NJ (US)

(21) Appl. No.: **12/147,042**

(22) Filed: **Jun. 26, 2008**

Related U.S. Patent Documents

Reissue of:

(64) Patent No.: **7,067,123**
Issued: **Jun. 27, 2006**
Appl. No.: **10/424,765**
Filed: **Apr. 29, 2003**

(51) **Int. Cl.**
A61K 35/32 (2006.01)

(52) **U.S. Cl.** **424/93.7**; 424/548

(58) **Field of Classification Search** ..... None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

3,400,199	A		9/1968	Balassa
3,551,560	A		12/1970	Theile
3,772,432	A	*	11/1973	Balassa 424/548
3,867,728	A		2/1975	Stubstad et al.
3,966,908	A		6/1976	Balassa
4,060,081	A		11/1977	Yannas et al.
4,172,128	A		10/1979	Thiele et al.
4,201,845	A		5/1980	Feder et al.
4,296,100	A		10/1981	Franco
4,378,347	A		3/1983	Franco
4,394,370	A		7/1983	Jefferies
4,400,833	A		8/1983	Kurland
4,442,655	A		4/1984	Stroetmann

(Continued)

FOREIGN PATENT DOCUMENTS

EP	0517030	A2	12/1992
EP	0522569	A1	1/1993
EP	0762903	B1	6/1995

(Continued)

OTHER PUBLICATIONS

(No Author)"Lyophilization" TechnoBusinesss–Solutions. (No publication date). Retrieved Jul. 1, 2009 from URL: <http://www.technobusiness–solutions.com/article–lyophilization1.html> 10 pages.*

(Continued)

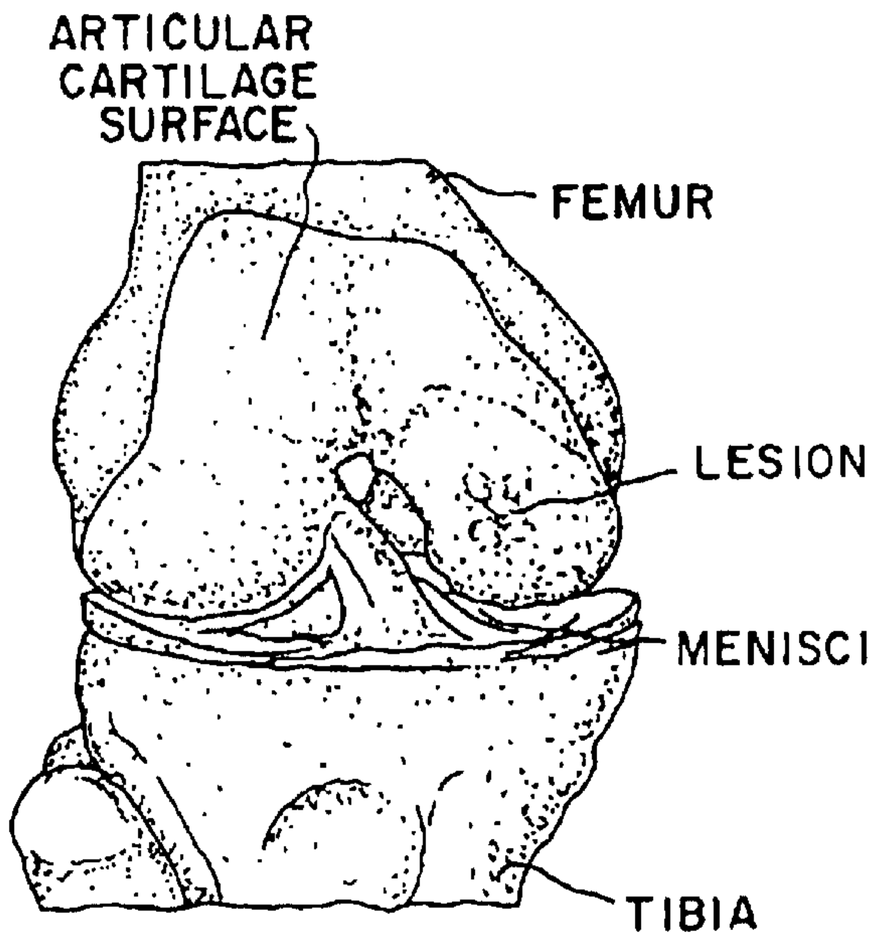
Primary Examiner—Allison M Ford

(74) *Attorney, Agent, or Firm*—Greenberg Traurig, LLP

(57) **ABSTRACT**

The invention is directed toward a sterile cartilage defect implant material comprising milled lyophilized allograft cartilage pieces ranging from 0.01 mm to 1.0 mm in size in a bioabsorbable carrier taken from a group consisting of sodium hyaluronate, hyaluronic acid and its derivatives, gelatin, collagen, chitosan, alginate, buffered PBS, Dextran or polymers with allogenic chondrocytes or bone marrow cells in an amount exceeding the natural occurrence of same in hyaline cartilage and adding a cell growth additive.

78 Claims, 1 Drawing Sheet



U.S. PATENT DOCUMENTS

4,458,678	A		7/1984	Yannas et al.
4,479,271	A		10/1984	Bolesky et al.
4,501,269	A		2/1985	Bagby
4,505,266	A		3/1985	Yannas et al.
4,600,574	A		7/1986	Lindner et al.
4,627,853	A		12/1986	Campbell et al.
4,642,120	A		2/1987	Nevo et al.
4,656,137	A		4/1987	Balassa
4,681,763	A		7/1987	Nathanson et al.
4,683,195	A		7/1987	Mullis et al.
4,683,202	A		7/1987	Mullis
4,757,017	A		7/1988	Cheung
4,776,173	A		10/1988	Kamarei et al.
4,776,853	A		10/1988	Klement et al.
4,795,467	A		1/1989	Piez et al.
4,801,299	A		1/1989	Brendel et al.
4,837,379	A		6/1989	Weinberg
4,846,835	A		7/1989	Grande
4,880,429	A		11/1989	Stone
4,902,508	A		2/1990	Badylak et al.
4,904,259	A		2/1990	Itay
4,932,973	A		6/1990	Gendler
4,950,296	A		8/1990	McIntyre
4,950,483	A		8/1990	Ksander et al.
4,955,911	A		9/1990	Frey et al.
4,963,146	A		10/1990	Li
4,965,188	A		10/1990	Mullis et al.
4,971,954	A		11/1990	Brodsky et al.
4,976,738	A		12/1990	Frey et al.
4,978,355	A		12/1990	Frey et al.
4,994,084	A		2/1991	Brennan
4,994,559	A		2/1991	Moscatelli et al.
5,002,583	A		3/1991	Pitaru et al.
5,007,934	A		4/1991	Stone
5,041,138	A		8/1991	Vacanti et al.
5,053,049	A		10/1991	Campbell
5,053,050	A		10/1991	Itay
5,067,964	A		11/1991	Richmond et al.
5,073,373	A		12/1991	O'Leary et al.
5,084,051	A		1/1992	Tormala et al.
5,118,512	A		6/1992	O'Leary
5,152,791	A		10/1992	Hakamatsuka et al.
5,155,214	A		10/1992	Baird et al.
5,191,067	A		3/1993	Lappi et al.
5,195,892	A		3/1993	Gershberg
5,206,023	A		4/1993	Hunziker
5,236,456	A		8/1993	O'Leary et al.
5,256,140	A		10/1993	Fallick
5,260,420	A		11/1993	Burnouf-Radosevich et al.
5,266,476	A		11/1993	Sussman et al.
5,270,300	A		12/1993	Hunziker
5,275,826	A		1/1994	Badylak et al.
5,284,155	A	*	2/1994	Treadwell et al. 600/562
5,290,558	A		3/1994	O'Leary et al.
5,298,254	A		3/1994	Prewett et al.
5,302,702	A		4/1994	Seddon et al.
5,306,304	A		4/1994	Gendler
5,306,311	A		4/1994	Stone et al.
5,310,883	A		5/1994	Seddon et al.
5,314,476	A		5/1994	Prewett et al.
5,326,357	A		7/1994	Kandel
5,329,846	A		7/1994	Bonutti
5,336,616	A		8/1994	Livesey et al.
5,338,772	A		8/1994	Bauer et al.
5,352,463	A		10/1994	Badylak et al.
5,354,557	A		10/1994	Oppermann et al.
5,356,629	A		10/1994	Sander et al.
5,368,858	A		11/1994	Hunziker
5,380,328	A		1/1995	Morgan
5,411,885	A		5/1995	Marx
5,425,769	A		6/1995	Snyders, Jr.
5,439,684	A		8/1995	Prewett et al.
5,439,818	A		8/1995	Fiddes et al.
5,443,950	A		8/1995	Naughton et al.
5,464,439	A		11/1995	Gendler
5,466,462	A		11/1995	Rosenthal et al.
5,491,220	A		2/1996	Seddon et al.
5,496,722	A		3/1996	Goodwin et al.
5,507,813	A		4/1996	Dowd et al.
5,512,460	A		4/1996	Nauro et al.
5,513,662	A		5/1996	Morse et al.
5,516,532	A		5/1996	Atala et al.
5,556,430	A		9/1996	Gendler
5,569,272	A		10/1996	Reed et al.
5,571,895	A		11/1996	Kurokawa et al.
5,576,288	A		11/1996	Lappi et al.
5,604,293	A		2/1997	Fiddes et al.
5,607,474	A		3/1997	Athanasiou et al.
5,614,496	A		3/1997	Dunstan et al.
5,618,925	A		4/1997	Dupont et al.
5,622,928	A		4/1997	Naruo et al.
5,624,463	A		4/1997	Stone et al.
5,631,011	A		5/1997	Wadstrom
5,632,745	A		5/1997	Schwartz
5,656,598	A		8/1997	Dunstan et al.
5,662,710	A		9/1997	Bonutti
5,679,637	A		10/1997	Lappi et al.
5,695,998	A		12/1997	Badylak et al.
5,700,476	A		12/1997	Rosenthal et al.
5,700,774	A		12/1997	Hattersley et al.
5,707,962	A		1/1998	Chen et al.
5,713,374	A		2/1998	Pachence et al.
5,716,413	A		2/1998	Walter et al.
5,723,331	A		3/1998	Tubo et al.
5,736,372	A		4/1998	Vacanti et al.
5,749,874	A		5/1998	Schwartz
5,759,190	A		6/1998	Vibe-Hansen et al.
5,769,899	A		6/1998	Schwartz et al.
5,770,417	A		6/1998	Vacanti et al.
5,782,835	A		7/1998	Hart et al.
5,782,915	A		7/1998	Stone
5,786,217	A		7/1998	Tubo et al.
5,800,537	A		9/1998	Bell
5,814,084	A		9/1998	Grivas et al.
5,842,477	A	*	12/1998	Naughton et al. 128/898
5,846,931	A		12/1998	Hattersley et al.
5,853,746	A		12/1998	Hunziker
5,855,620	A		1/1999	Bishopric et al.
5,859,208	A		1/1999	Fiddes et al.
5,863,296	A		1/1999	Orton
5,863,297	A		1/1999	Walter et al.
5,866,415	A		2/1999	Villeneuve
5,876,452	A		3/1999	Athanasiou et al.
5,888,219	A		3/1999	Bonutti
5,893,888	A		4/1999	Bell
5,899,936	A		5/1999	Goldstein
5,904,716	A		5/1999	Gendler
5,906,827	A		5/1999	Khouri et al.
5,910,315	A		6/1999	Stevenson et al.
5,916,265	A		6/1999	Hu
5,948,429	A		9/1999	Bell et al.
5,955,438	A		9/1999	Pitaru et al.
5,964,805	A		10/1999	Stone
5,968,556	A		10/1999	Atala et al.
5,972,368	A		10/1999	McKay
5,972,385	A		10/1999	Liu et al.
5,974,663	A		11/1999	Ikeda et al.
5,989,269	A		11/1999	Vibe-Hansen et al.
5,989,289	A		11/1999	Coates et al.
5,989,866	A		11/1999	Deisher et al.
5,998,170	A		12/1999	Arakawa et al.

6,001,352 A	12/1999	Boyan et al.
6,005,161 A	12/1999	Brekke et al.
6,013,853 A	1/2000	Athanasiou et al.
6,017,348 A	1/2000	Hart et al.
6,025,334 A	2/2000	Dupont et al.
6,025,538 A	2/2000	Yaccarino, III
6,027,743 A	2/2000	Khouri et al.
6,030,635 A	2/2000	Gertzman et al.
6,037,171 A	3/2000	Larsson
6,039,762 A	3/2000	McKay
6,060,640 A	5/2000	Pauley et al.
6,074,663 A	6/2000	Delmotte et al.
6,080,194 A	6/2000	Pachence et al.
6,090,996 A	7/2000	Li
6,090,998 A	7/2000	Grooms et al.
6,096,081 A	8/2000	Grivas et al.
6,096,347 A	8/2000	Geddes et al.
6,110,209 A	8/2000	Stone
6,110,482 A	8/2000	Khouri et al.
6,123,731 A	9/2000	Boyce et al.
6,132,472 A	10/2000	Bonutti
6,143,293 A	11/2000	Weiss et al.
6,156,068 A	12/2000	Walter et al.
6,165,486 A	12/2000	Marra et al.
6,165,487 A	12/2000	Ashkar et al.
6,180,605 B1	1/2001	Chen et al.
6,183,737 B1	2/2001	Zaleske et al.
6,189,537 B1	2/2001	Wolfinbarger, Jr.
6,197,586 B1	3/2001	Bhatnagar et al.
6,200,347 B1	3/2001	Anderson et al.
6,221,854 B1	4/2001	Radomsky
6,231,607 B1	5/2001	Ben-Bassat et al.
6,235,316 B1	5/2001	Adkisson
6,242,247 B1	6/2001	Rieser et al.
6,251,143 B1	6/2001	Schwartz et al.
6,258,778 B1	7/2001	Rodgers et al.
6,261,586 B1	7/2001	McKay
6,267,786 B1	7/2001	Stone
6,270,528 B1	8/2001	McKay
6,274,090 B1	8/2001	Coelho et al.
6,274,663 B1	8/2001	Hosokawa et al.
6,274,712 B1	8/2001	Springer et al.
6,280,473 B1	8/2001	Lemperle et al.
6,281,195 B1	8/2001	Rueger et al.
6,283,980 B1	9/2001	Vibe-Hansen et al.
6,293,970 B1	9/2001	Wolfinbarger, Jr.
6,294,187 B1	9/2001	Boyce et al.
6,294,359 B1	9/2001	Fiddes et al.
6,303,585 B1	10/2001	Spiro et al.
6,305,379 B1	10/2001	Wolfinbarger, Jr.
6,306,174 B1	10/2001	Gie et al.
6,306,424 B1	10/2001	Vyakarnam et al.
6,310,267 B1	10/2001	Rapp
6,319,712 B1	11/2001	Meenen et al.
6,333,029 B1	12/2001	Vyakarnam et al.
6,352,558 B1	3/2002	Spector
6,352,971 B1	3/2002	Deisher et al.
6,361,565 B1	3/2002	Bonutti
6,376,244 B1	4/2002	Atala
6,379,367 B1	4/2002	Vibe-Hansen et al.
6,379,385 B1	4/2002	Kalas et al.
6,383,221 B1	5/2002	Scarborough
6,387,693 B2	5/2002	Rieser et al.
6,398,811 B1	6/2002	McKay
6,398,816 B1	6/2002	Breitbart et al.
6,398,972 B1	6/2002	Blasetti et al.
6,432,436 B1	8/2002	Gertzman et al.
6,437,018 B1	8/2002	Gertzman et al.
6,440,141 B1	8/2002	Philippon
6,440,427 B1	8/2002	Wadstrom
6,440,444 B2	8/2002	Boyce et al.
6,454,811 B1	9/2002	Sherwood et al.
6,458,144 B1	10/2002	Morris et al.
6,458,158 B1	10/2002	Anderson et al.
6,458,375 B1	10/2002	Gertzman et al.
6,468,314 B2	10/2002	Schwartz
6,471,993 B1	10/2002	Shastri et al.
6,475,175 B1	11/2002	Rivera et al.
6,486,377 B2	11/2002	Rapp
6,488,033 B1	12/2002	Cerundolo
6,489,165 B2	12/2002	Bhatnagar
6,497,726 B1	12/2002	Carter et al.
6,503,277 B2	1/2003	Bonutti
6,511,511 B1	1/2003	Slivka et al.
6,511,958 B1	1/2003	Atkinson et al.
6,514,514 B1	2/2003	Atkinson et al.
6,520,964 B2	2/2003	Tallarida et al.
6,530,956 B1	3/2003	Mansmann
6,534,084 B1	3/2003	Vyakarnam et al.
6,541,024 B1	4/2003	Kadiyala et al.
6,548,729 B1	4/2003	Seelich et al.
6,569,172 B2	5/2003	Asculai et al.
6,576,015 B2	6/2003	Geistlich et al.
6,582,960 B1	6/2003	Martin et al.
6,591,581 B2	7/2003	Schmieding
6,592,598 B2	7/2003	Vibe-Hansen et al.
6,592,599 B2	7/2003	Vibe-Hansen et al.
6,599,300 B2	7/2003	Vibe-Hansen et al.
6,599,301 B2	7/2003	Vibe-Hansen et al.
6,599,515 B1	7/2003	Delmotte
6,623,963 B1	9/2003	Muller et al.
6,626,950 B2	9/2003	Brown et al.
6,630,000 B1	10/2003	Bonutti
6,632,247 B2	10/2003	Boyer, II et al.
6,652,592 B1	11/2003	Grooms et al.
6,652,593 B2	11/2003	Boyer, II et al.
6,652,872 B2	11/2003	Nevo et al.
6,662,805 B2	12/2003	Frondoza et al.
6,666,892 B2	12/2003	Hiles et al.
6,686,184 B1	2/2004	Anderson et al.
6,689,747 B2	2/2004	Filvaroff et al.
6,696,073 B2	2/2004	Boyce et al.
6,712,851 B1	3/2004	Lemperle et al.
6,727,224 B1	4/2004	Zhang et al.
6,730,314 B2	5/2004	Jeschke et al.
6,734,018 B2	5/2004	Wolfinbarger, Jr. et al.
6,743,232 B2	6/2004	Overaker et al.
6,752,834 B2	6/2004	Geistlich et al.
6,761,739 B2	7/2004	Shepard
6,761,887 B1	7/2004	Kavalkovich et al.
6,767,369 B2	7/2004	Boyer, II et al.
6,776,800 B2	8/2004	Boyer, II et al.
6,783,712 B2	8/2004	Slivka et al.
6,808,585 B2	10/2004	Boyce et al.
6,815,416 B2	11/2004	Carney et al.
6,838,440 B2	1/2005	Stiles
6,841,150 B2	1/2005	Halvorsen et al.
6,852,114 B2	2/2005	Cerundolo
6,852,125 B2	2/2005	Simon et al.
6,852,331 B2	2/2005	Lai et al.
6,855,167 B2	2/2005	Shimp et al.
6,855,169 B2	2/2005	Boyer, II et al.
6,858,042 B2	2/2005	Nadler et al.
6,866,668 B2	3/2005	Giannetti et al.
6,884,428 B2	4/2005	Binette et al.
6,890,354 B2	5/2005	Steiner et al.
6,893,462 B2	5/2005	Buskirk et al.
6,902,578 B1	6/2005	Anderson et al.
6,911,212 B2	6/2005	Gertzman et al.
6,932,977 B2	8/2005	Heidaran et al.
6,933,326 B1	8/2005	Griffey et al.
6,933,328 B2	8/2005	Schacht

6,949,252	B2	9/2005	Mizuno et al.
6,989,034	B2	1/2006	Hammer et al.
6,995,013	B2	2/2006	Connelly et al.
7,009,039	B2	3/2006	Yayon et al.
7,018,416	B2	3/2006	Hanson et al.
7,033,587	B2	4/2006	Halvorsen et al.
7,041,641	B2	5/2006	Rueger et al.
7,044,968	B1	5/2006	Yaccarino, III et al.
7,045,141	B2	5/2006	Merboth et al.
7,048,750	B2	5/2006	Vibe-Hansen et al.
7,048,762	B1	5/2006	Sander et al.
7,048,765	B1	5/2006	Grooms et al.
7,067,123	B2	6/2006	Gomes et al.
7,070,942	B2	7/2006	Heidaran et al.
7,078,232	B2	7/2006	Konkle et al.
7,108,721	B2	9/2006	Huckle et al.
RE39,321	E	10/2006	MacPhee et al.
7,115,146	B2	10/2006	Boyer, II et al.
7,125,423	B2	10/2006	Hazebrouck
7,132,110	B2	11/2006	Kay et al.
7,137,989	B2	11/2006	Asculai et al.
7,141,072	B2	11/2006	Coeistlich
7,156,880	B2	1/2007	Evans et al.
7,157,428	B2	1/2007	Kusanagi et al.
7,163,563	B2	1/2007	Schwartz et al.
7,166,133	B2	1/2007	Evans et al.
7,179,299	B2	2/2007	Edwards et al.
7,182,781	B1	2/2007	Bianchi et al.
7,201,917	B2	4/2007	Malaviya et al.
7,217,294	B2	5/2007	Kusanagi et al.
7,220,558	B2	5/2007	Luyten et al.
7,241,316	B2	7/2007	Evans et al.
7,252,987	B2	8/2007	Bachalo et al.
7,264,634	B2	9/2007	Schmieding
7,288,406	B2	10/2007	Bogin et al.
7,291,169	B2	11/2007	Hodorek
7,297,161	B2	11/2007	Fell
7,316,822	B2	1/2008	Binette et al.
7,323,011	B2	1/2008	Shepard et al.
7,323,445	B2	1/2008	Zhang et al.
7,335,508	B2	2/2008	Yayon et al.
7,338,492	B2	3/2008	Singhatat
7,338,524	B2	3/2008	Fell et al.
7,358,284	B2	4/2008	Griffey et al.
7,361,195	B2	4/2008	Schwartz et al.
7,365,051	B2	4/2008	Paulista et al.
7,371,400	B2	5/2008	Borenstein et al.
7,416,889	B2	8/2008	Ciombor et al.
7,468,075	B2	12/2008	Lang et al.
7,468,192	B2	12/2008	Mizuno et al.
7,479,160	B2	1/2009	Branch et al.
7,485,310	B2	2/2009	Luyten et al.
7,488,348	B2	2/2009	Truncale et al.
7,513,910	B2	4/2009	Buskirk et al.
7,531,000	B2	5/2009	Hodorek
7,537,617	B2	5/2009	Bindsell et al.
7,537,780	B2	5/2009	Mizuno et al.
7,550,007	B2	6/2009	Malinin
7,563,455	B2	7/2009	McKay
7,563,769	B2	7/2009	Bogin et al.
7,601,173	B2	10/2009	Messerli et al.
7,608,113	B2	10/2009	Boyer, II et al.
7,621,963	B2	11/2009	Simon et al.
7,622,438	B1	11/2009	Lazarov et al.
7,622,562	B2	11/2009	Thorne et al.
7,628,851	B2	12/2009	Armitage et al.
7,632,311	B2	12/2009	Seedhom et al.
7,638,486	B2	12/2009	Lazarov et al.
7,642,092	B2	1/2010	Maor
7,648,700	B2	1/2010	Vignery et al.
7,648,965	B2	1/2010	Vignery et al.
7,658,768	B2	2/2010	Miller et al.
7,662,184	B2	2/2010	Edwards et al.
7,666,230	B2	2/2010	Orban et al.
2001/0005592	A1	6/2001	Bhatnagar et al.
2001/0006634	A1	7/2001	Zaleske et al.
2001/0010023	A1	7/2001	Schwartz et al.
2001/0011131	A1	8/2001	Luyten et al.
2001/0016646	A1	8/2001	Rueger et al.
2001/0018619	A1	8/2001	Enzerink et al.
2001/0020188	A1	9/2001	Sander
2001/0021875	A1	9/2001	Enzerink et al.
2001/0031254	A1	10/2001	Bianchi et al.
2001/0039457	A1	11/2001	Boyer, II et al.
2001/0039458	A1	11/2001	Boyer, II et al.
2001/0043940	A1	11/2001	Boyce et al.
2001/0051834	A1	12/2001	Frondoza et al.
2002/0009805	A1	1/2002	Nevo et al.
2002/0016592	A1	2/2002	Branch et al.
2002/0035401	A1	3/2002	Boyce et al.
2002/0042373	A1	4/2002	Carney et al.
2002/0045940	A1	4/2002	Giannetti et al.
2002/0055783	A1	5/2002	Tallarida et al.
2002/0072806	A1	6/2002	Buskirk et al.
2002/0082704	A1	6/2002	Cerundolo
2002/0099448	A1	7/2002	Hiles et al.
2002/0106393	A1	8/2002	Bianchi et al.
2002/0111695	A1	8/2002	Kandel
2002/0120274	A1	8/2002	Overaker et al.
2002/0138143	A1	9/2002	Grooms et al.
2002/0177224	A1	11/2002	Madry et al.
2002/0192263	A1	12/2002	Merboth et al.
2003/0021827	A1	1/2003	Malaviya et al.
2003/0023316	A1	1/2003	Brown et al.
2003/0032961	A1	2/2003	Pelo et al.
2003/0033021	A1	2/2003	Plouhar et al.
2003/0033022	A1	2/2003	Plouhar et al.
2003/0036797	A1	2/2003	Malaviya et al.
2003/0036801	A1	2/2003	Schwartz et al.
2003/0039695	A1	2/2003	Geistlich et al.
2003/0040113	A1	2/2003	Mizuno et al.
2003/0044444	A1	3/2003	Malaviya et al.
2003/0049299	A1	3/2003	Malaviya et al.
2003/0050709	A1	3/2003	Noth et al.
2003/0055502	A1	3/2003	Lang et al.
2003/0078617	A1	4/2003	Schwartz et al.
2003/0099620	A1	5/2003	Zaleske et al.
2003/0144743	A1	7/2003	Edwards et al.
2003/0229400	A1	12/2003	Masuda et al.
2003/0236573	A1	12/2003	Evans et al.
2004/0028717	A1	2/2004	Sittinger et al.
2004/0033212	A1	2/2004	Thomson et al.
2004/0039447	A1	2/2004	Simon et al.
2004/0044408	A1	3/2004	Hungerford et al.
2004/0062753	A1	4/2004	Rezania et al.
2004/0078090	A1	4/2004	Binette et al.
2004/0102850	A1	5/2004	Shepard
2004/0115172	A1	6/2004	Bianchi et al.
2004/0134502	A1	7/2004	Mizuno et al.
2004/0138748	A1	7/2004	Boyer, II et al.
2004/0143344	A1	7/2004	Malaviya et al.
2004/0151705	A1	8/2004	Mizuno et al.
2004/0166169	A1	8/2004	Malaviya et al.
2004/0170610	A1	9/2004	Slavin et al.
2004/0175826	A1	9/2004	Maor
2004/0192605	A1	9/2004	Renwen et al.
2004/0193268	A1	9/2004	Hazebrouck
2004/0197311	A1	10/2004	Brekke et al.
2004/0197373	A1	10/2004	Gertzman et al.
2004/0219182	A1	11/2004	Gomes et al.
2004/0220574	A1	11/2004	Pelo et al.
2004/0230303	A1	11/2004	Gomes et al.

2004/0243242	A1	12/2004	Sybert et al.
2005/0004672	A1	1/2005	Pafford et al.
2005/0020500	A1	1/2005	Shen et al.
2005/0027307	A1	2/2005	Schwartz et al.
2005/0043814	A1	2/2005	Kusanagi et al.
2005/0064042	A1	3/2005	Vunjak-Novakovia et al.
2005/0074476	A1	4/2005	Gendler et al.
2005/0074481	A1	4/2005	Brekke et al.
2005/0089544	A1	4/2005	Khouri et al.
2005/0101957	A1	5/2005	Buskirk et al.
2005/0112761	A1	5/2005	Halvorsen et al.
2005/0129668	A1	6/2005	Giannetti et al.
2005/0152882	A1	7/2005	Kizer et al.
2005/0159820	A1	7/2005	Yoshikawa et al.
2005/0159822	A1	7/2005	Griffey et al.
2005/0196460	A1	9/2005	Malinin
2005/0209705	A1	9/2005	Niederauer et al.
2005/0222687	A1	10/2005	Vunjak-Novakovia et al.
2005/0228498	A1	10/2005	Andres
2005/0240281	A1	10/2005	Slivka et al.
2005/0251268	A1	11/2005	Truncale
2005/0260612	A1	11/2005	Padmini et al.
2005/0261681	A9	11/2005	Branch et al.
2005/0261767	A1	11/2005	Anderson et al.
2005/0288796	A1	12/2005	Awad et al.
2006/0030948	A1	2/2006	Manrique et al.
2006/0060209	A1	3/2006	Shepard
2006/0099234	A1	5/2006	Winkler
2006/0111778	A1	5/2006	Michalow
2006/0167483	A1	7/2006	Asculai et al.
2006/0178748	A1	8/2006	Dinger, III et al.
2006/0200166	A1	9/2006	Hanson et al.
2006/0210643	A1	9/2006	Truncale et al.
2006/0216323	A1	9/2006	Knaack et al.
2006/0216822	A1	9/2006	Mizuno et al.
2006/0235534	A1	10/2006	Gertzman et al.
2006/0247790	A1	11/2006	McKay
2006/0247791	A1	11/2006	McKay et al.
2006/0251631	A1	11/2006	Adkisson, IV et al.
2006/0276907	A1	12/2006	Boyer, II et al.
2007/0009610	A1	1/2007	Syring
2007/0014867	A1	1/2007	Kusanagi et al.
2007/0026030	A1	2/2007	Gill et al.
2007/0036834	A1	2/2007	Pauletti et al.
2007/0041950	A1	2/2007	Leatherbury et al.
2007/0055377	A1	3/2007	Hanson et al.
2007/0065943	A1	3/2007	Smith et al.
2007/0067032	A1	3/2007	Felt et al.
2007/0083266	A1	4/2007	Lang
2007/0093896	A1	4/2007	Malinin
2007/0093912	A1	4/2007	Borden
2007/0098759	A1	5/2007	Malinin
2007/0100045	A1	5/2007	Hodorek
2007/0113951	A1	5/2007	Huang
2007/0128155	A1	6/2007	Seyedin
2007/0134291	A1	6/2007	Ting
2007/0135917	A1	6/2007	Malinin
2007/0135918	A1	6/2007	Malinin
2007/0135928	A1	6/2007	Malinin
2007/0148242	A1	6/2007	Vilei et al.
2007/0162121	A1	7/2007	Tarrant et al.
2007/0168030	A1	7/2007	Edwards et al.
2007/0172506	A1	7/2007	Nycz et al.
2007/0179601	A1	8/2007	Hodorek et al.
2007/0185585	A1	8/2007	Bracy et al.
2007/0276506	A1	11/2007	Troxel
2007/0299517	A1	12/2007	Davisson et al.
2007/0299519	A1	12/2007	Schmieding
2008/0015709	A1	1/2008	Evans et al.
2008/0027546	A1	1/2008	Semler et al.
2008/0031915	A1	2/2008	Becerra Ratia et al.
2008/0038314	A1	2/2008	Hunziker
2008/0039939	A1	2/2008	Iwamoto et al.
2008/0039954	A1	2/2008	Long et al.
2008/0039955	A1	2/2008	Hunziker
2008/0051889	A1	2/2008	Hodorek
2008/0065210	A1	3/2008	McKay
2008/0077251	A1	3/2008	Chen et al.
2008/0119947	A1	5/2008	Huckle et al.
2008/0125863	A1	5/2008	McKay
2008/0125868	A1	5/2008	Branemark
2008/0138414	A1	6/2008	Hunckle et al.
2008/0153157	A1	6/2008	Yao et al.
2008/0154372	A1	6/2008	Peckham
2008/0167716	A1	7/2008	Schwartz et al.
2008/0183300	A1	7/2008	Seedhom et al.
2008/0305145	A1	12/2008	Shelby et al.
2009/0043389	A1	2/2009	Vunjak-Novakovic et al.
2009/0069901	A1	3/2009	Truncale et al.
2009/0069904	A1	3/2009	Picha
2009/0076624	A1	3/2009	Rahaman et al.
2009/0081276	A1	3/2009	Alsberg et al.
2009/0099661	A1	4/2009	Bhattacharya et al.
2009/0117652	A1	5/2009	Luyten et al.
2009/0131986	A1	5/2009	Lee et al.
2009/0149893	A1	6/2009	Semler et al.
2009/0210057	A1	8/2009	Liao et al.
2009/0226523	A1	9/2009	Behnam et al.
2009/0280179	A1	11/2009	Neumann et al.
2009/0299475	A1	12/2009	Yamamoto et al.
2009/0312805	A1	12/2009	Lang et al.
2009/0312842	A1	12/2009	Bursac et al.
2009/0319051	A9	12/2009	Nycz et al.
2010/0021521	A1	1/2010	Xu et al.
2010/0036492	A1	2/2010	Hung et al.
2010/0036503	A1	2/2010	Chen et al.

FOREIGN PATENT DOCUMENTS

EP	0762903	A1	12/1995
EP	0517030	B1	9/1996
EP	0739631	A2	10/1996
EP	0784985	A1	7/1997
EP	0968012	A1	9/1998
EP	1719531	A2	5/2001
EP	1237511	B1	6/2001
EP	1237511	A1	6/2001
EP	1127581	A1	8/2001
EP	1181908	A1	2/2002
EP	1234552	A1	8/2002
EP	1234555	A2	8/2002
EP	0739631	B1	3/2003
EP	1181908	B1	12/2003
EP	1384452	A1	1/2004
EP	1234555	A3	6/2004
EP	1618178	A1	11/2004
EP	1127581	B1	6/2005
EP	1561481	A2	8/2005
EP	1618178	B1	1/2006
EP	1234552	B1	8/2006
EP	0968012	B1	9/2006
EP	1719463	A1	11/2006
EP	1719532	A2	11/2006
EP	1234555	B1	2/2007
EP	0762903	B2	8/2007
EP	1537883	B1	4/2008
GB	2102811	A1	2/1983
SU	1454423	A1	1/1989
WO	WO 84/04880	A1	12/1984
WO	90/01342	A1	2/1990
WO	93/16739	A1	9/1993
WO	WO 94/03584	A1	2/1994
WO	95/25748	A1	9/1995

WO	WO 95/33502	A1	12/1995
WO	95/24310	A1	8/1996
WO	WO 98/14222	A1	4/1998
WO	WO 98/41246	A2	9/1998
WO	98/43686	A1	10/1998
WO	WO 99/09914	A1	3/1999
WO	WO 99/11298	A2	3/1999
WO	99/15209	A1	4/1999
WO	WO 99/21497	A1	5/1999
WO	WO 99/22747		5/1999
WO	WO 99/48541	A1	9/1999
WO	WO 99/52572	A1	10/1999
WO	99/56797	A1	11/1999
WO	WO 00/40177	A1	7/2000
WO	00/47114	A1	8/2000
WO	01/07595	A2	2/2001
WO	01/38357	A2	5/2001
WO	01/39788	A2	6/2001
WO	01/46416	A1	6/2001
WO	WO 01/043667	A1	6/2001
WO	02/18546	A2	3/2002
WO	02/22779	A2	3/2002
WO	02/95019	A1	3/2002
WO	02/36732	A2	5/2002
WO	WO 02/058484	A2	8/2002
WO	WO 02/064180	A1	8/2002
WO	02/077199	A2	10/2002
WO	02/095019	A1	11/2002
WO	WO 03/007805	A2	1/2003
WO	WO 03/007805	A3	1/2003
WO	03/007873	A2	1/2003
WO	WO 03/007879	A2	1/2003
WO	WO 03/007879	A3	1/2003
WO	03/012053	A2	2/2003
WO	03/079985	A2	10/2003
WO	03/087160	A1	10/2003
WO	03/094835	A2	11/2003
WO	2004/067704	A2	8/2004
WO	2004/069298	A1	8/2004
WO	WO 2004/075940	A1	9/2004
WO	WO 2004/096983	A2	11/2004
WO	WO 2004/096983	A3	11/2004
WO	WO 2004/103224	A1	12/2004
WO	2005058207	A1	6/2005
WO	WO 2005/110278	A3	11/2005
WO	WO 2005/110278	A2	11/2005
WO	WO 2006/042311	A3	4/2006
WO	WO 2006/042311	A2	4/2006
WO	2006/050213	A2	5/2006
WO	02/36732	A3	9/2006
WO	2006/113586	A2	10/2006
WO	03/094835	A3	12/2006
WO	WO 2007/024238	A1	3/2007
WO	2006/113586	A3	9/2007
WO	2008/013763	A2	1/2008
WO	WO 2008/021127	A2	2/2008
WO	2008/038287	A2	4/2008
WO	2008/013763	A3	6/2008
WO	2008/081463	A2	7/2008
WO	2008/038287	A3	9/2008
WO	WO 2008/106254	A2	9/2008
WO	WO 2009/076164	A2	6/2009
WO	WO 2009/111069	A3	9/2009

OTHER PUBLICATIONS

Hunziker, "Articular Cartilage Repair: Basic Science and Clinical Progress. A Review of the Current Status and Prospects", Osteoarthritis and Cartilage 2001, vol. 10, No. 6, pp. 432–463.

Chen et al., "Repair of Articular Cartilage Defects: Part I. Basic Science of Cartilage Healing", The American Journal of Orthopedics, Jan. 1999, pp. 31–33.

Chen et al., "Repair of Articular Cartilage Defects: Part II. Treatment Options", The American Journal of Orthopedics, Feb. 1999, pp. 88–96.

Buckwalter, "Articular Cartilage Injuries", Clinical Orthopaedics and Related Research, 2002, No. 402, pp. 21–37.

Nixon et al., "New Horizons in Articular Cartilage Repair", Proceedings of the Annual Convention of the AAEP, 2001, vol. 47, pp. 217–226.

Tsumaki et al., "Role of CDMP–1 in Skeletal Morphogenesis: Promotion of Mesenchymal Cell Recruitment and Chondrocyte Differentiation", J. Cell Biol., Jan. 1999, vol. 144, No. 1, 161–173.

Feczko et al., "Experimental Results of Donor Site Filling for Autologous Osteochondral Mosaicplasty", Arthroscopy: The Journal of Arthroscopic and Related Surgery, vol. 19, No. 7 (Sep. 2003), pp. 755–761.

Peretti et al., "Cell–Based Bonding of Articular Cartilage: An Extended Study", Journal of Biomedical Materials Research, 64A, 2003, pp. 517–524.

Peretti et al., "Cell–Based Tissue–Engineered Allogeneic Implant for Cartilage Repair", Tissue Engineering, 2000, vol. 6, No. 5, pp. 567–576.

Bugbee, "Fresh Osteochondral Allografting", Operative Techniques in Sports Medicine, Apr. 2000, vol. 8, No. 2, pp. 158–162.

Jackson et al., "Cartilage Substitutes: Overview of Basic Science & Treatment Options", Journal of American Academy of Orthopaedic Surgeons, vol. 9, Jan./Feb. 2001, pp. 37–52.

Verbruggen et al., "Repair Function in Organ Cultured Human Cartilage. Replacement of Enzymatically Removed Proteoglycans During Longterm Organ Culture", The Journal of Rheumatology, 12:4, 1985, pp. 665–674.

Glowacki, "Engineered Cartilage, Bone, Joints and Menisci—Potential for Temporomandibular Joint Reconstruction", Cells Tissues Organs, vol. 169, Issue 3, 2001, pp. 302–308.

Peretti et al., "A Biomechanical Analysis of an Engineered Cell–Scaffold Implant for Cartilage Repair", Annals of Plastic Surgery, 2001, vol. 46, No. 5, pp. 533–537.

Peretti et al., "A Biomechanical Analysis of a Chondrocyte–Based Repair Model of Articular Cartilage", Tissue Engineering, Aug. 1, 1999, vol. 5, No. 4, pp. 317–326.

Peretti et al., "In Vitro Bonding of Pre–seeded Chondrocytes", Sport Sciences for Health, May 1, 2007, vol. 2, No. 1, pp. 29–33.

Peretti et al., "Bonding of Cartilage Matrices with Cultured Chondrocytes: An Experimental Model", Journal of Orthopedic Research, Jan. 1998, vol. 16, No. 1, pp. 89–95.

Nettles et al., "In Situ Crosslinkable Hyaluronan For Articular Cartilage Repair", 50th Annual Meeting of the Orthopaedic Research Society, (Mar. 2004) Paper No. 0202.

Nettles et al., "Photocrosslinkable Hyaluronan As a Scaffold for Articular Cartilage Repair", Annals of Biomedical Engineering, vol. 32, No. 3, Mar. 2004, pp. 391–397.

Girotto et al., "Tissue–specific gene expression in chondrocytes grown on three–dimensional hyaluronic acid scaffolds", Biomaterials, vol. 24 (2003), pp. 3265–3275.

Gertzman et al., "A pilot study evaluating sodium hyaluronate as a carrier for freeze–dried demineralized bone powder", Cell and Tissue Banking, vol. 2, 2001, pp. 87–94.

Trzeciak et al., "Evaluation of Cartilage Reconstruction by Means of Autologous Chondrocyte Versus Periosteal Graft Transplantation: An Animal Study", Transplantation Proceedings, vol. 38 (2006), pp. 305–311.

Brighton et al., "Articular Cartilage Preservation and Storage—I. Application of Tissue Culture Techniques to the Storage of Viable Articular Cartilage", Arthritis and Rheumatism, vol. 22, No. 10 (Oct. 1979) pp. 1093–1101.

Mahadev et al., "Autogenous Osteochondral Morselised Grafts for Full Thickness Osteochondral Defects in the Knee Joints of Pigs", Singapore Medical Journal, 2001, vol. 42(9), pp. 410–416.

Hunziker, "Articular Cartilage Structure in Humans and Experimental Animals", *Articular Cartilage and Osteoarthritis,* Raven Press, ed., 1992, pp. 183–199.

Diduch et al., "Joint Repair: Treatment Options for Articular Cartilage Injury" Orthopedic Technology Review (2002) 4:24–27.

Stone, et al., "One–step American Technique of Articular Cartilage Paste Grafting to Traumatic and Arthritic Defects in the Knee Joint (2–7 Years Follow Up)", downloaded from http://www.stoneclinic.com/onestep.htm, publication date unavailable. Downloaded Apr. 4, 2008.

Gilbert, et al., "Decellularization of Tissue and Organs", Biomaterials (2006) 27:3675–3683.

Non–final Office Action mailed on Feb. 6, 2007 in connection with U.S. Appl. No. 10/438,883.

Non–final Office Action mailed on Nov. 5, 2004 in connection with U.S. Appl. No. 10/438,883.

Office Action issued on Apr. 24, 2007 in connection with Australian Patent Application No. 2004235291.

Non–final Office Action mailed on May 3, 2005 in connection with U.S. Appl. No. 10/438,883.

Final Office Action mailed on Oct. 18, 2005 in connection with U.S. Appl. No. 10/438,883.

USPTO Communication mailed Oct. 9, 2007 in connection with U.S. Appl. No. 10/438,883.

Non–final Office Action mailed on Apr. 19, 2007 in connection with U.S. Appl. No. 11/151,270.

Final Office Action mailed on Oct. 9, 2007 in connection with U.S. Appl. No. 11/151,270.

Advisory Action mailed on Dec. 27, 2007 in connection with U.S. Appl. No. 11/151,270.

Office Action mailed Feb. 7, 2008 in connection with U.S. Appl. No. 10/815,778.

Non–final Office Action mailed on Feb. 20, 2007 in connection with U.S. Appl. No. 10/960,960.

Final Office Action mailed on Sep. 28, 2007 in connection with U.S. Appl. No. 10/960,960.

Non–final Office Action mailed on Dec. 18, 2007 in connection with U.S. Appl. No. 11/081,103.

Office Action issued on Nov. 7, 2007 in connection with New Zealand Patent Application No. 543665.

U.S. Appl. No. 12/010,984, filed Jan. 31, 2008 titled Cartilage Repair Mixture Containing Allograft Chondroctypes.

U.S. Appl. No. 11/657,042, filed Jan. 24, 2007 titled Two Piece Cancellous Construct for Cartilage Repair.

U.S. Appl. No. 12/043,001, filed Mar. 5, 2008 Cancellous Construct with Support Ring for Repair of Osteochondral Defects.

U.S. Appl. No. 12/079,629, filed Mar. 26, 2008 Titled Cartilage Implant Plug with Fibrin Glue and Method for Implantation.

International Search Report issued in connection with International Patent Application No. PCT/US2004/010957 Application on Nov. 1, 2004.

International Preliminary Report on Patentability issued on Nov. 18, 2005 in connection with International Patent Application No. PCT/US2004/010957.

International Search Report issued in connection with International Patent Application No. PCT/US2005/030610 on Apr. 7, 2006.

Written Opinion issued on Apr. 7, 2006 in connection with International Patent Application No. PCT/US2005/030610.

International Search Report issued on Sep. 21, 2006 in connection with International Patent Application No. PCT/US2005/036878.

International Preliminary Report on Patentability issued on Apr. 17, 2007 2006 in connection with International Patent Application No. PCT/US2005/036878.

Office Action issued on Sep. 8, 2006 in connection with European Patent Application No. 04749924.9.

Supplementary European Search Report issued on Jun. 28, 2006 in connection with European Patent Application No. 04749924.9.

International Search Report issued in connection with International Patent Application No. PCT/US2005/008798 on Jun. 19, 2006.

Written Opinion issued in connection with International Patent Application No. PCT/US2005/008798 on Jun. 19, 2006.

International Preliminary Report on Patentability issued in connection with International Patent Application No. PCT/US2005/008798 on Nov. 1, 2006.

International Search Report issued in connection with International Patent Application No. PCT/US2004/010956 on Oct. 28, 2005.

Written Opinion issued in connection with International Patent Application No. PCT/US2004/010956 on Oct. 28, 2005.

International Preliminary Report on Patentability issued on Nov. 18, 2005 in connection with International Patent Application No. PCT/US2004/010956.

International Patent Application No. PCT/US2008/051796 filed Jan. 23, 2008 titled Two Piece Cancellous Construct for Cartilage Repair.

Written Opinion issued in connection with International Patent Application No. PCT/US2004/010957 on Nov. 1, 2004.

International Preliminary Report on Patentability issued on Feb. 26, 2008 in connection with International Patent Application No. PCT/US2005/030610.

Written Opinion issued in connection with International Patent Application No. PCT/US2005/036878 on Sep. 21, 2006.

Hoffman, "Hydrogels for Biomedical Applications", Advanced Drug Delivery Reviews, 2002, vol. 43, pp. 3–12.

Dahlberg et al., "Demineralized Allogeneic Bone Matrix for Cartilage Repair", Journal of Orthopaedic Research, 1991, vol. 9, pp. 11–19.

Lu et al., "Minced Cartilage without Cell Culture Serves as an Effective Intraoperative Cell Source for Cartilage Repair", Journal of Orthopaedic Research, Jun. 2006, vol. 24, pp. 1261–1270.

Stone et al., "Articular Cartilage Paste Grafting to Full–Thickness Articular Cartilage Knee Joint Lesions: A 2– to 12–Year Follow–up", Arthroscopy: The Journal of Arthoscopic and Related Surgery, Mar. 2006, vol. 22, No. 3, pp. 291–299.

Newman, "Articular Cartilage Repair", American Journal of Sports Medicine, 1998, vol. 26, No. 2, pp. 309–324.

Brittberg et al., "Treatment of Deep Cartilage Defects in the Knee with Autologous Chondrocyte Transplantation", New England Journal of Medicine, Oct. 6, 1994, vol. 331, No. 14, pp. 889–895.

Nixon et al., "Enhanced Repair of Extensive Articular Defects by Insulin–like Growth Factor–I–Laden Fibrin Composites", Journal of Orthopaedic Research, 1999; 17:475–487.

International Cartilage Repair Society, "Cartilage Injury Evaluation Package", www.cartilage.org, 2000.

Richardson et al., "Repair of Human Articular Cartilage After Implantation of Autologous Chondrocytes", Journal of Bone and Joint Surgery [Br], 1999, 81–B:1064–1068.

Brittberg et al., "Autologous Chondrocytes Used for Articular Cartilage Repair: An Update", Clinical Orthopaedics and Related Research, 2001; No. 391 Suppl: S337–S348.

Peterson et al., "Two– to 9–year Outcome After Autologous Chondrocyte Transplantation of the Knee", Clinical Orthopaedic and Related Research, 2000; No. 374: 212–234.

Peterson et al., "Autologous Chondrocyte Transplantation: Biomechanics and Long–term Durability", American Journal of Sports Medicine, 2002, vol. 30, No. 1, pp. 2–12.

Messner et al., "Cartilage Repair: A Critical Review", Acta Orthopaedic Scandinavica, 1996, vol. 67, No. 5, pp. 523–529.

Messner et al., "The Long–term Prognosis for Severe Damage to Weight–bearing Cartilage in the Knee: A 14–year Clinical and Radiographic Follow–up in 28 Young Athletes", Acta Orthopaedic Scandinavica, 1996, vol. 67, No. 2, pp. 165–168.

Buckwalter et al., "Articular Cartilage: Degeneration and Osteoarthritis, Repair, Regeneration, and Transplantation", AAOS Instructional Course Lectures, 1998; 47:487–504.

Breinan et al., "Effect of Cultured Autologous Chondrocytes on Repair of Chondral Defects in a Canine Model", Journal of Bone and Joint Surgery [Am], Oct. 1997; vol. 79–A, No. 10, 1439–1451.

Breinan et al., "Autologous Chondrocyte Implantation in a Canine Model: Change in Composition of Reparative Tissue with Time", Journal of Orthopaedic Research, 2001; 19:482–492.

Brittberg et al., "Rabbit Articular Cartilage Defects Treated with Autologous Cultured Chondrocytes", Clinical Orthopaedics and Related Research, 1996; 326:270–283.

Nehrer et al., "Chondrocyte–seeded Collagen Matrices Implanted in a Chondral Defect in a Canine Model", Biomaterials, 1998; 19:2313–2328.

Vunjak–Novakovic et al., "Bioreactor Cultivation Conditions Modulate the Composition and Mechanical Properties of Tissue–Engineered Cartilage", Journal of Orthopaedic Research, 1999; 17:130–138.

Bursac, "Collagen Network Contributions to Structure–Function Relationships in Cartilaginous Tissues in Compression" (Dissertation), Boston University College of Engineering, 2002.

Gooch et al., "IGF–I and Mechanical Environment Interact to Modulate Engineered Cartilage Development", Biochemical and Biophysical Research Communications, 2001; 286:909–915.

Pei et al., "Growth Factors for Sequential Cellular De– and Re–differentiation in Tissue Engineering", Biochemical and Biophysical Research Comunications, 2002; 294:149–154.

Obradovic et al., "Integration of Engineered Cartilage", Journal of Orthopaedic Research, 19:1089–1097, 2001.

Schaefer et al., "Tissue Engineered Composites for tha Repair of Large Osteochondral Defects", Arthritis & Rheumatism, 46(9): 2524–2534 (2002).

Pei et al., "Bioreactors Mediate the Effectiveness of Tissue Engineering Scaffolds", The FASEB Journal, 16:1691–1694, published online (Aug. 7, 2002), 10.1096/fj.02–0083fje.

Madry et al., "Gene Transfer of a Human Insulin–like Growth Factor I cDNA Enhances Tissue Engineering of Cartilage", Human Gene Therapy, 13: 1621–1630 (Sep. 1, 2002).

Pearson et al. (eds.), American Association of Tissue Banks, Standards for Tissue Banking, 2008 (12^{th} ed.), pp. 53–56, 86–88.

Ornits et al., "Protein Family Review: Fibroblast Growth Factors", Genome Biology (2001) 2(3): reviews 3005.1–3005.12, http://genomebiology.com/2001/2/3/reviews/3005.1.

Loeser et al., "Basic Fibroblast Growth Factor Inhibits the Anabolic of Insulin–like Growth Factor 1 and Osteogenic Protein 1 in Adult Human Articular Chondrocytes", Arthritis & Rheumatism, vol. 52, No. 12 (Dec. 2005), pp. 3910–3917.

Kato et al., "Fibroblast Growth Factor is an Inhibitor of Chondrocyte Terminal Defferentiation", Journal of Biological Chemistry, vol. 265, No. 10 (Apr. 5, 1990) pp. 5903–5909.

Andrés et al., "A Pro–Inflammatory Signature Mediates FGF2–induced Angiogenesis", Journal of Cellular and Molecular Medicine, (2008).

Burger et al., "Fibroblast growth factor receptor–1 is expressed by endothelial progenitor cells", Blood, vol. 100, No. 10 (Nov. 15, 2002) 3527–35.

Baird, "Fibroblast growth factors: activities and significance of non–neurotrophin neurotrophic growth factors", Current Opinions in Neurobiology, (1994) 4:78–86.

Mazué et al., "Preclinical and Clinical Studies with Recombinant Human Basic Fibroblast Growth Factor", Annals New York Academy of Sciences, (1991) 329–340.

Aviles et al., "Testing clinical therapeutic angiogenesis using basic fibroblast growth factor (FGF–2)", British Journal of Pharmacology (2003) 140: 637–646.

Nolan et al., "Living Bone Grafts", BMJ, vol. 304, Jun. 13, 1992, pp. 1520 and 1521.

Osteo Sponge product information, Bacterin International Inc., May 2005.

A non–final Office Action mailed on Jun. 8, 2009 in connection with U.S. Appl. No. 11/481,955.

A non–final Office Action mailed on Jul. 9, 2008 in connection with U.S. Appl. No. 11/151,270.

A final Office Action mailed on Nov. 13, 2008 in connection with U.S. Appl. No. 10/815,778.

A non–final Office Action mailed on Jul. 2, 2009 in connection with U.S. Appl. No. 10/815,778.

A non–final Office Action mailed on May 18, 2009 in connection with U.S. Appl. No. 11/657,042.
U.S. Appl. No. 12/381,072, filed Mar. 5, 2009 entitled "Cancellous Constructs, Cartilage Particles and Combinations of Cancellous Constructs and Cartilage Particles".
A final Office Action mailed on Sep. 19, 2008 in connection with U.S. Appl. No. 11/081,103.
U.S. Appl. No. 12/508,892, filed Jul. 24, 2009 entitled "Cancellous Constructs with Support Ring for Repair of Osteochondral Defects".
An International Search Report issued on Jun. 23, 2009 in connection with International Patent Application No. PCT/US2008/051796.
A Written Opinion issued on Jun. 23, 2009 in connection with International Patent Application No. PCT/US2008/051796.
An International Preliminary Report on Patentability issued on Jul. 28, 2009 in connection with International Patent Application No. PCT/US2008/051796.
An International Search Report issued on Jul. 6, 2009 in connection with International Patent Application No. PCT/US2008/085522.
A Written Opinion issued on Jul. 6, 2009 in connection with International Patent Application No. PCT/US2008/085522.
An International Search Report issued on Jul. 6, 2009 in connection with International Patent Application No. PCT/US2009/001459.
A Written Opinion issued on Jul. 6, 2009 in connection with International Patent Application No. PCT/US2009/001459.
Canadian Office Action issued on Aug. 24, 2009 in connection with Canadian Patent Application No. 2,563,082.
http://www.stoneclinic.com/articularcartilagepastegrafting, no date.
http://www.technobusiness–solutions.com/article–lyophilization1.html, published Feb. 12, 2002.
Non–final Office Action mailed on Jul. 22, 2009 in connection with U.S. Appl. No. 12/010,984.
Non–final Office Action mailed on Jun. 3, 2009 in connection with U.S. Appl. No. 11/081,103.
Non–Final Office Action for U.S. Appl. No. 11/081,103, mailed Jan. 14, 2010.
Final Office Action for U.S. Appl. No. 11/481,955, mailed Jan. 7, 2010.
Crescenzi et al., "Hyaluronan Linear and Crosslinked Derivatives as Potential/Actual Biomaterials", in Hyaluronan (2002), vol. 1 (Chemical, Biochemical and Biological Aspects), J. F. Kennedy et al., Ed., pp. 261–268.
Michielen et al., "Novel Biomaterials Based on Cross–linked Hyaluronan: Structural Investigations", in Hyaluronan (2002), vol. 1 (Chemical, Biochemical and Biological Aspects), J. F. Kennedy et al., Ed., pp. 269–276.
U.S. Appl. No. 12/696,366, filed Jan. 29, 2010.
U.S. Appl. No. 12/657,207, filed Jan. 14, 2010.
Office Action dated Jan. 14, 2010, received in U.S. Appl. No. 11/081,103, filed on Mar. 16, 2005.
Yee, Cindy J. et al., (2000) Analysis of fibroblast growth factor receptor 3 S249C mutation in cervical carcinoma. Journal of the National Cancer Institute 92(22):1848–1849.
Zhang, Jiandong et al., (1991) Three–dimensional structure of human basic fibroblast growth factor, a structural homolog of interleukin 1 Beta. Proc Natl Acad Sci. USA 88(8):3446–3450.
Zhu, Hengyi et al., (1995) Glu–96 of basic fibroblast growth factor is essential for high affinity receptor binding. Journal Of Biological Chemistry 270(37):21869–21874.
Zhu, Hengyi et al., (1997) Analysis of high–affinity binding determinants in the receptor binding epitope of basic fibroblast growth factor. Protein Engineering 10(4):417–421.
Carr, M. E. Jr. and Alving, B. M. (1995) Effect of fibrin structure on plasmin–mediated dissolution of plasma clots. Blood Coag, Fibrinol. 6(6):567–573.
Carr, Marcus E. (1998) Fibrin formed in plasma is composed of fibers more massive than those formed from purified fibrinogen. Thromb. Haemost. 59(3):535–539.
Cook, James L. et al., (2003) Biocompatibility of three–dimensional chondrocyte grafts in large tibial defects of rabbits. Am J Vet Res. 64(1):12–20.
Gao, Jizong et al., (2002) Repair of osteochondral defect with tissue–engineered two–phase composite material of injectable calcium phosphate and hyaluronan sponge. Tissue Engin. Part A 8(5):827–837.
Gruber, Reinhard et al., (2002) Platelets stimulate proliferation of bone cells: involvement of platelet–derived growth factor, microparticles and membranes. Clin Oral Implants Res. 13(5):529–535.
Haisch, A. et al., (2000) Preparation of a pure autologous biodegradable fibrin matrix for tissue engineering. Med Biol Eng Comput. 38(6):686–689.
Itokazu, M. et al., (1997) The sustained release of antibiotic from freeze–dried fibrin–antibioticcompound and efficacies in a rat model of osteomyelitis. Infection 25(6):359–363.
Sims, C. Derek et al., (1998) Tissue engineered neocartilage using plasma derived polymer substrates and chondrocytes. Plastic & Recon. Surg. 101(6):1580–1585.
"Young's Modulus," Entry on http://en.wikipedia.org. accessed Oct. 27, 2005. 3 pages.
Bradford, Marion M. (1976) A Rapid and Sensitive Method for the Quantitation of Microgram Quantities of Protein Utilizing the Principle of Protein–Dye Binding. Analytical Biochemistry 72(1–2):248–254.
Matsuda et al. (1995) In Vivo Chondrogenesis in Collagen Sponge Sandwiched by Perichondrium. J. Biomater. Sci. Polymer Ed., vol. 7, No. 3, pp. 221–229.
Fujisato et al., (1996) Effect of basic fibroblast growth factor on cartilage regeneration in chondrocyte–seeded collagen sponge scaffold. Biomaterials, vol. 17, No. 2, pp. 155–162.
Non–Final Office Action mailed Apr. 15, 2010 in connection with U.S. Appl. No. 12/079,629.
Non–Final Office Action mailed Apr. 12, 2010 in connection with U.S. Appl. No. 12/191,490.
Non–Final Office Action mailed Apr. 15, 2010 in connection with U.S. Appl. No. 11/657,042.
International Preliminary Report on Patentability for PCT/US2009/001459, mailed on May 12, 2010.
Atala et al., Injectable alginate seeded with chondrocytes as a potential treatment for vesicoureteral reflux, J. of Urology 150(2 Pt 2):745–7 (1993).
International Preliminary Report on Patentability for PCT/US2008/085522, mailed on Jun. 17, 2010.
Nettles et al. (Mar. 2004), "In Situ Crosslinkable Hyaluronan For Articular Cartilage Repair", 50th Annual Meeting of the Orthopaedic Research Society, Paper No. 0202.
Final Office Action for U.S. Appl. No. 11/081,103, mailed Aug. 11, 2010.
Non–final Office Action for U.S. Appl. No. 12/010,984, mailed Aug. 16, 2010.

Abraham, Judith A. et al., (1986) Human Basic Fibroblast Growth Factor: Nucleotide Sequence And Genomic Organization. EMBO Journal 5(10):2523–2528.

Agrawal, Sudhir et al., (1991) Pharmacokinetics. Biodistribution, And Stability Of Oligodeoxynucleotide Phosphorothioates In Mice. Proc Natl Acad Sci. USA 88(17):7595–7599.

Arakawa, Tsutomu et al., (1993) Production and Characterization of an Analog of Acidic Fibroblast Growth Factor With Enhanced Stability and Biological Activity. Protein Engineering 6(5):541–546.

Bailly, Karine et al., (2000) Uncoupling of cell proliferation and differentiation activities of basic fibroblast growth factor. FASEB Journal 14(2):333–343.

Bange, Johannes et al., (2002) Cancer progression and tumor cell motility are associated with the FGFR4 Arg388 Allele. Cancer Research 62(3):840–846.

Bork, Peer (2000) Powers and pitfalls in sequence analysis: The 70% hurdle. Genome Res. 10(4):398–400.

Bork, Peer and Bairoch, Amnon (1996) Go hunting in sequence databases but watch out for the traps. Trends in Genetics 12(10):425–427.

Brenner, Steven E. (1999) Errors in genome annotation. Trends in Genetics 15(4):132–133.

Cappellen, David et al., (1999) Frequent activating mutations of FGFR3 In human bladder arid cervix carcinomas. Nature Genetics 23(1):18–20.

Chusho, Hideki et al., (2001) Dwarfism and earlydeath in mice lacking C–type Natriuretic Peptide. Proc Natl Acad Sci. 98(7):4016–4021.

Coughlin, Shaun R. et al., (1988) Acidic and basic fibroblast growth factors stimulate tyrosine kinase activity in vivo. J Biol Chem. 263(2):988–993.

Dell'Accio, Francesco et al., (2001) Molecular markers predictive of the capacity of expanded human articular chondrocytes to form stable cartilage in vivo, Arthritis Rheum. 44(7):1608–19.

Doerks, Tobias et al., (1998) Protein annotation: detective work for function prediction. Trends Genet. 14(6):248–250.

Dvorakova, Dana et al., (2001) Changes in the expression of FGFR3 in patients with chronic myeloid leukaemia receiving transplant of allogeneic peripheral blood stem cells__ British Journal Haematology 13(3):832–835.

Eriksson, A. Elisabeth et al., (1991) Three–dimensional structure of human basic fibroblast growth factor. Proc. Natl. Acad. Sci. USA 88:3441–3445 (XP002936511).

Ezzat Shereen et al., (2002) Targeted expression of A Human pituitary tumor–derived isoform of FGF Receptor–4 Recapitulates Pituitary Tumorigenesis. Journal of Clinical Investigation 109(1):69–77.

Faham, Salem et al., (1998) Diversity does make a difference: fibroblast growth factor—Heparin Interactions. Curr Opin Struct Biol 8(5):578–586.

Fingl, Edward and Woodbury, Dixon M.(1975) Chapter I: General Priciples; In: The Pharmacological Basis of Therapeutics. Fifth edition. Goodman, Louis S. and Gilman, Alfred editors. 1:1–45.

Gargiulo, B. J. et al., (2002) Phenotypic modulation of human articular chondrocytes by bistratene A. Eur Cell Mater. 3:9–18.

Givol, David and Yayon, Avner (1992) Complexity of FGF receptors: genetic basis for structural diversity and functional specificity FASEB J. 6(15):3362–3369.

Hecht, H. J. et al., (2000) Structure of fibroblast growth factor 9 shows a symmetric dimer with unique receptor–and heparin–binding interfaces. Acta Cryst. D57:378–384.

Johnson, Daniel E. and Williams, Lewis T. (1993) Structural and functional diversity in the FGF receptor multigene family. Adv Cancer Res. 60:1–41.

Kirikoshi, Hiroyuki et al., (2000) Molecular cloning and characterization of Human FGF–20 on chromosome 8p21.3–p22. Biochem Biophys Res Commun. 274(2):337–343.

Kuroda, S. et al., (1999) Anabolic effect of aminoterminally truncated Fibroblast Growth Factor 4 (FGF4) on bone. Bone 25:(4):431–437.

Nakatake, Yuhki et al., (2001) Identification of a novel fibroblast growth factor. FGF–22, preferentially expressed in the inner root sheath of the hair follicle. Biochim Biophys Acta. 1517(3):460–463.

Ngo, J. Thomas et al., (1994) Computational complexity, protein structure prediction, and the Levithal Paradox. In: The Protein Folding Problem and Tertiary Structure Prediction. K. Merz Jr. and S. Le Grand, Editors. 433–506.

Nishimura, Tetsuya et al., (2000) Identification Of a Novel FGF, FGF–21, Preferentially Expressed In The Liver. Biochim Biophys Acta 1492(1):203–206.

Okada–Ban, Mai et al., (2000) Fibroblast growth factor–2. International Journal of Biochemistry & Cell Biology 32 (3):263–267.

Olsen, Shaun K. (2003) Fibroblast growth factor (FGF) homologous factors share structural but not functional homology with FGFs J. Biol Chem. 278(36); pp. 34226–34236.

Ornitz, David M. et al., (1996) Receptor specificity of the fibroblast growth factor family. J Biol Chem. 271(25)15292–7.

Ornitz, David M. (2000) FGFs, heparan sulfate and FGFRs: Complex interactions essential for development. Bio Essays 22:108–112.

Pellegrini, Luca et al., (2000) Crystal structure of fibroblast growth factor receptor ectodomain bound to ligand and heparin. Nature 407(6807):1029–1034.

Pillai, Omathanu and Panchagnula, Ramesh (2001) Polymers in drug delivery. Curr Opin Chem Biol 5 (4):447–451.

Plotnikov, Alexander N. et al., (1999) Structural basis for FGF receptor dimerization and activation. Cell 98 (5):641–650.

Plotnikov, Alexander N. et al., (2000) Crystal structures of two FGF–FGFR complexes reveal the determinants of ligand–receptor specificity. Cell 101(4):413–424.

Sahni, Malika et al., (1999) FGF signaling inhibits chondrocyte proliferation and regulates bone development through the STAT–1 pathway. Genes Dev. 13:1361–1366.

Schlessinger, Joseph et al., (2000) Crystal structure of a ternary FGF–FGFR–1 Heparin complex reveals a dual role for heparin in FGFR binding and dimerization. Mol Cell 6(3):743–750.

Schmal, H. et al., (2007) bFGF influences human articular chondrocytes differentiation. Cytotherapy 9(2):184–93.

Seno, Masaharu et al., (1990) Carboxyl–terminal structure of basic fibroblast growth factor significantly contributes to its affinity for Heparin. Eur J Biochem. 188:239–245.

Shano; Zhang–Qiang et al., (2006) Effects of intramyocardial administration of slow–release basic fibroblast growth factor on angiogenesis and ventricular remodelling in a rat infarct model. Circ. J. 70(4):471–477.

Skolnik, Jeffrey and Fetrow, Jacquelyn S. (2000) From genes to protein structure and function: novel applications of computational approaches in the genomic era. Trends Bio Technol. 18(1):34–39.

Sleeman, Matthew et al., (2001) Identification of a new fibroblast growth factor receptor, FGFR5. Gene 271 (2):171–182.

Smith, Temple and Zhang, Xiaolin (1997) The challenges of genome sequence annotation or The devil is in the details, Nat Biotecehnol. 15(12):1222–1223.

Springer, Barry A. et al., (1994) Identification and Concerted Function of Two Receptors Binding Surfaces on Basic Fibroblast Growth Factor Required for Mitogenesis. The Journal of Biological Chemistry 269(43):26879–26884.

Stauber, Deborah J. et al., (2000) Structural interactions of fibroblast growth factor receptor with its ligands. Proc Natl Acad Sci USA 97(1):49–54.

Vajo, Zoltan et al., (2000) The Molecular and Genetic Basis of Fibroblast Growth Factor Receptor 3 Disorders: The Achondroplasia Family of Skeletal Dysplasias, Muenke Craniosynostosis, and Crouzon Syndrome with Acanthosis Nigricans. Endocrine Rev. 21(1):23–39.

Wells, James A. (1990) Additivity of mutational effects in proteins. Biochemistry 29(37):8509–8517.

Yamashita, Tetsuo et al., (2000) Identification of a novel fibroblast growth factor, FGF–23, preferentially expressed in the ventrolateral thalamic nucleus of the brain. Biochemical and Biophysical Research Communications 277 (2):494–498.

Yayon, Avner et al., (1991) Cell surface, heparin–like molecules are required for binding of basic fibroblast growth factor to its high affinity receptor. Cell 64(4):841–848.

International Search Report and Written Opinion for PCT/US2010/000108, mailed Aug. 24, 2010.

International Patent Application No. PCT/US2009/000108, filed Jan. 14, 2010, entitled “Cartilage Particle Tissue Mixtures Optionally Combined With a Cancellous Construct”.

Final Office Action mailed Mar. 15, 2010 in connection with U.S. Appl. No. 10/815,778.

Final Office Action mailed Mar. 22, 2010 in connection with U.S. Appl. No. 12/010,984.

U.S. App. No. 12/881,988, filed Sep. 14, 2010.

U.S. Appl. No. 12/924,132, filed Sep. 21, 2010.

Temenoff et al., “Review: Tissue engineering for regeneration of articular cartilage”, Biomaterials 21 (2000) pp. 431–440.

Hunziker, “Articular cartilage repair: are the intrinsic biological constraints undermining this processiInsuperable?”, Osteoarthritis and Cartilage 7 (1999) pp. 15–28.

* cited by examiner

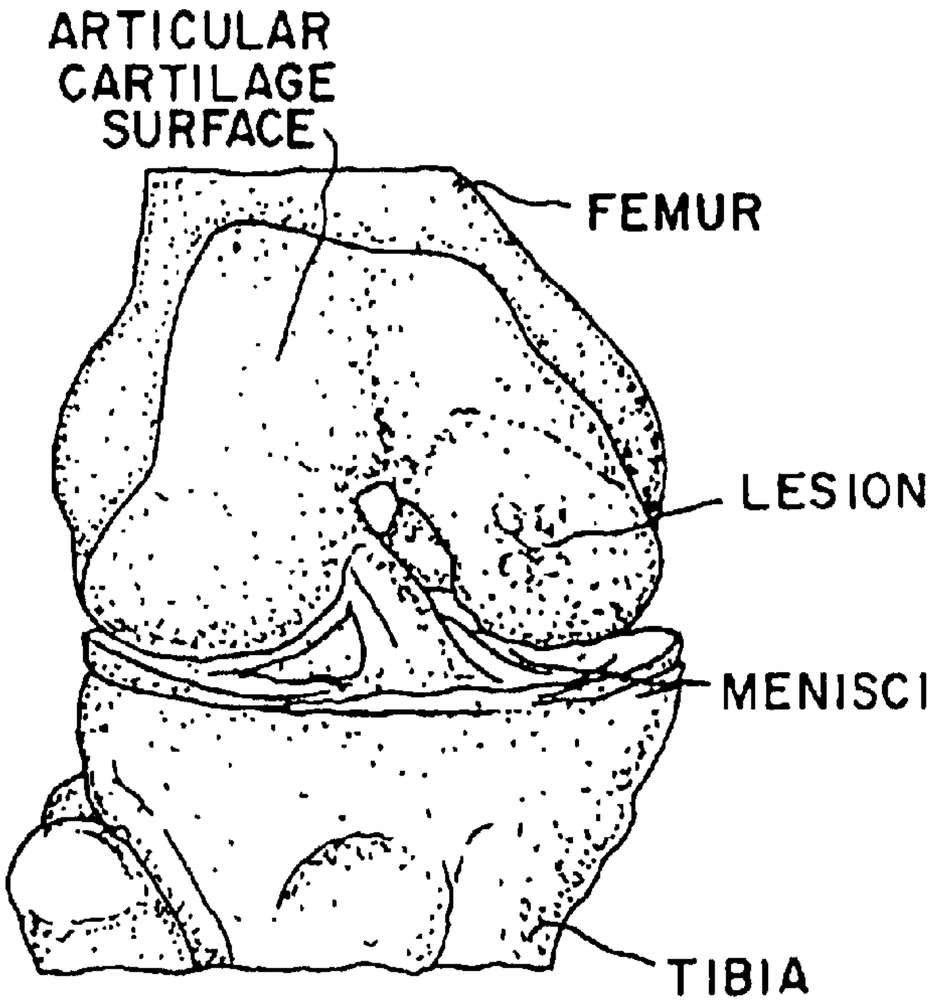


Fig. 1

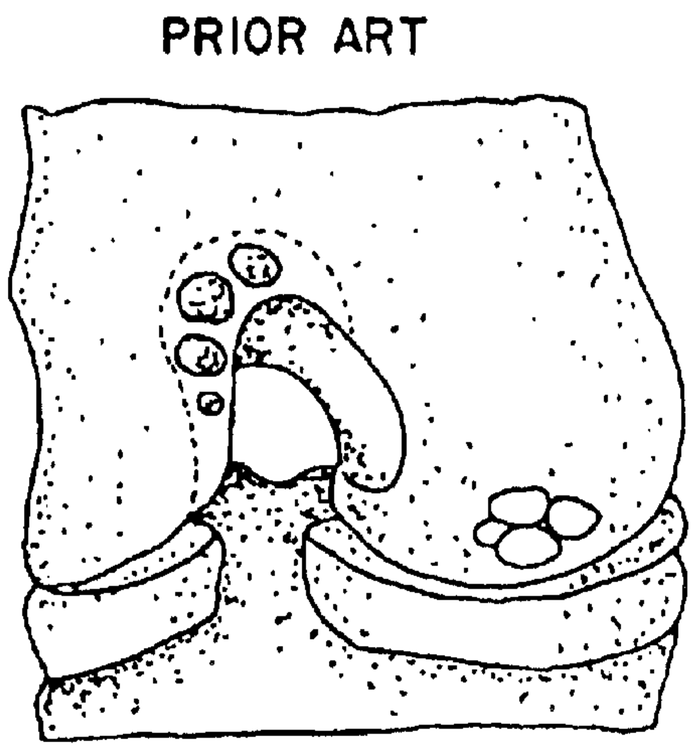


Fig. 2

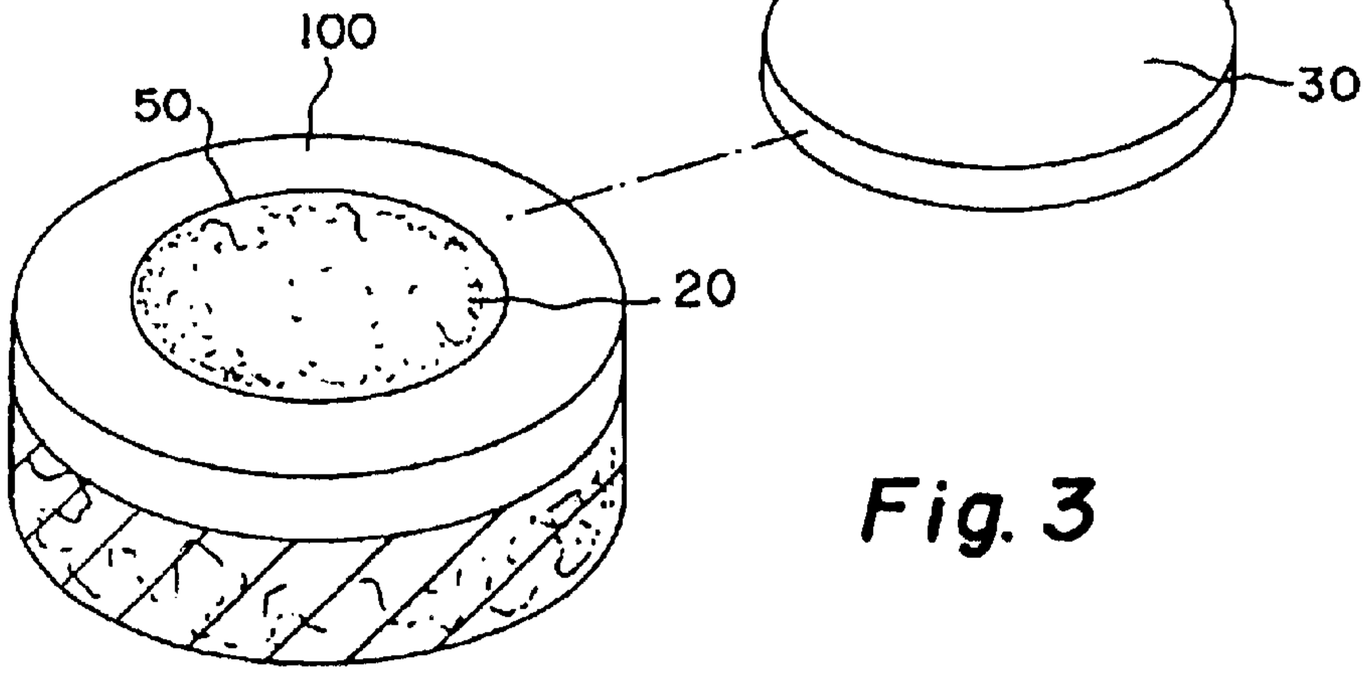


Fig. 3

GLUE FOR CARTILAGE REPAIR

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

RELATED APPLICATIONS

[There is no related application.] *The instant application is a reissue of application Ser. No. 10/424,765, filed Apr. 29, 2003, and issued as U.S. Pat. No. 7,067,123.*

1. Field of Invention

The present invention is generally directed toward an implant and is more specifically directed toward a paste or gel implant material for a cartilage defect.

2. Background of the Invention

Articular cartilage injury and degeneration present medical problems to the general population which are addressed by orthopedic surgeons. Every year in the United States, over 500,000 arthroplastic or joint repair procedures are performed. These include approximately 125,000 total hip and 150,000 total knee arthroplasties and over 41,000 open arthroscopic procedures to repair cartilaginous defects of the knee.

In the knee joint, the articular cartilage tissue forms a lining which faces the joint cavity on one side and is linked to the subchondral bone plate by a narrow layer of calcified cartilage tissue on the other. Articular cartilage (hyaline cartilage) consists primarily of extracellular matrix with a sparse population of chondrocytes distributed throughout the tissue. Articular cartilage is composed of chondrocytes, type II collagen fibril network, proteoglycans and water. Active chondrocytes are unique in that they have a relatively low turnover rate and are sparsely distributed within the surrounding matrix. The collagens give the tissue its form and tensile strength and the interaction of proteoglycans with water give the tissue its stiffniess to compression, resilience and durability. The hyaline cartilage provides a low friction bearing surface over the bony parts of the joint. If the lining becomes worn or damaged resulting in lesions, joint movement may be painful or severely restricted. Whereas damaged bone typically can regenerate successfully, hyaline cartilage regeneration is quite limited because of it's limited regenerative and reparative abilities.

Articular cartilage lesions generally do not heal, or heal only partially under certain biological conditions due to the lack of nerves, blood vessels and a lymphatic system. The limited reparative capabilities of hyaline cartilage usually results in the generation of repair tissue that lacks the structure and biomechanical properties of normal cartilage. Generally, the healing of the defect results in a fibrocartilaginous repair tissue that lacks the structure and biomedical properties of hyaline cartilage and degrades over the course of time. Articular cartilage lesions are frequently associated with disability and with symptoms such as joint pain, locking phenomena and reduced or disturbed function. These lesions are difficult to treat because of the distinctive structure and function of hyaline cartilage. Such lesions are believed to progress to severe forms of osteoarthritis. Osteoarthritis is the leading cause of disability and impairment in middle-aged and older individuals, entailing significant economic, social and psychological costs. Each year, osteoarthritis accounts for as many as 39 million physician visits and more than 500,000 hospitalizations. By the year 2020, arthritis is expected to affect almost 60 million persons in the United States and to limit the activity of 11.6 million persons.

There are many current therapeutic methods being used. None of these therapies has resulted in the successful regeneration of hyaline-like tissue that withstands normal joint loading and activity over prolonged periods. Currently, the techniques most widely utilized clinically for cartilage defects and degeneration are not articular cartilage substitution procedures, but rather lavage, arthroscopic debridement, and repair stimulation. The direct transplantation of cells or tissue into a defect and the replacement of the defect with biologic or synthetic substitutions presently accounts for only a small percentage of surgical interventions. The optimum surgical goal is to replace the defects with cartilage-like substitutes so as to provide pain relief, reduce effusions and inflammation, restore function, reduce disability and postpone or alleviate the need for prosthetic replacement.

Lavage and arthroscopic debridement involve irrigation of the joint with solutions of sodium chloride, Ringer or Ringer and lactate. The temporary pain relief is believed to result from removing degenerative cartilage debris, proteolytic enzymes and inflammatory mediators. These techniques provide temporary pain relief, but have little or no potential for further healing.

Repair stimulation is conducted by means of drilling, abrasion arthroplasty or microfracture. Penetration into the subchondral bone induces bleeding and fibrin clot formation which promotes initial repair, however, the tissue formed is fibrous in nature and not durable. Pain relief is temporary as the tissue exhibits degeneration, loss of resilience, stiffness and wear characteristics over time.

The periosteum and perichondrium have been shown to contain mesenchymal progenitor cells capable of differentiation and proliferation. They have been used as grafts in both animal and human models to repair articular defects. Few patients over 40 years of age have obtained good clinical results, which most likely reflects the decreasing population of osteochondral progenitor cells with increasing age. There have also been problems with adhesion and stability of the grafts, which result in their displacement or loss from the repair site.

Transplantation of cells grown in culture provides another method of introducing a new cell population into chondral and osteochondral defects. Carticel® is a commercial process to culture a patient's own cartilage cells for use in the repair of cartilage defects in the femoral condyle marketed by Genzyme Biosurgery in the United States and Europe. The procedure uses arthroscopy to take a biopsy from a healthy, less loaded area of articular cartilage. Enzymatic digestion of the harvested tissue releases the cells that are sent to a laboratory where they are grown for a period ranging from 2–5 weeks. Once cultivated, the cells are injected during a more open and extensive knee procedure into areas of defective cartilage where it is hoped that they will facilitate the repair of damaged tissue. An autologous periosteal flap with cambium layer is used to seal the transplanted cells in place and act as a mechanical barrier. Fibrin glue is used to seal the edges of the flap. This technique preserves the subchondral bone plate and has reported a high success rate. Proponents of this procedure report that it produces satisfactory results, including the ability to return to demanding physical activities, in more than 90% of patients and that biopsy specimens of the tissue in the graft sites show hyaline-like cartilage repair. More work is needed to assess the function and durability of the new tissue and determine whether it improves joint function and delays or prevents joint degeneration. As with the perichondrial graft, patient/donor age may compromise the success of this procedure as chondrocyte population decreases with increasing age. Dis-

advantages to this procedure include the need for two separate surgical procedures, potential damage to surrounding cartilage when the periosteal patch is sutured in place, the requirement of demanding microsurgical techniques, and the expensive cost of the procedure which is currently not covered by insurance.

Osteochondral transplantation or mosaicplasty involves excising all injured or unstable tissue from the articular defect and creating cylindrical holes in the base of the defect and underlying bone. These holes are filled with autologous cylindrical plugs of healthy cartilage and bone in a mosaic fashion. The osteochondral plugs are harvested from a lower weight-bearing area of lesser importance in the same joint. This technique, shown in Prior Art FIG. **2**, can be performed as arthroscopic or open procedures. Reports of results of osteochondral plug autografts in a small number of patients indicate that they decrease pain and improve joint function, however, long-term results have not been reported. Factors that can compromise the results include donor site morbidity, effects of joint incongruity on the opposing surface of the donor site, damage to the chondrocytes at the articular margins of the donor and recipient sites during preparation and implantation, and collapse or settling of the graft over time. The limited availability of sites for harvest of osteochondral autografts restricts the use of this approach to treatment of relatively small articular defects and the healing of the chondral portion of the autograft to the adjacent articular cartilage remains a concern.

Transplantation of large allografts of bone and overlying articular cartilage is another treatment option that involves a greater area than is suitable for autologous cylindrical plugs, as well as for a non-contained defect. The advantages of osteochondral allografts are the potential to restore the anatomic contour of the joint, lack of morbidity related to graft harvesting, greater availability than autografts and the ability to prepare allografts in any size to reconstruct large defects. Clinical experience with fresh and frozen osteochondral allografts shows that these grafts can decrease joint pain, and that the osseous portion of an allograft can heal to the host bone and the chondral portion can function as an articular surface. Drawbacks associated with this methodology in the clinical situation include the scarcity of fresh donor material and problems connected with the handling and storage of frozen tissue. Fresh allografts carry the risk of immune response or disease transmission. Musculoskeletal Transplant Foundation (MTF) has preserved fresh allografts in a media that maintains a cell viability of 50% for 35 days for use as implants. Frozen allografts lack cell viability and have shown a decreased amount of proteoglycan content which contribute to deterioration of the tissue.

A number of patents in the prior art show the use of bone putty, pastes or gels to fill bone defects. U.S. Pat. No. 5,290,558 issued Mar. 1, 1994 discloses a flowable demineralized bone powder composition using an osteogenic bone powder with large particle size ranging from about 0.1 to about 1.2 cm. mixed with a low molecular weight polyhydroxy compound possessing from 2 to about 18 carbons including a number of classes of different compounds such as monosaccharides, disaccharides, water dispersible oligosaccharides and polysaccharides.

A bone gel is disclosed in the U.S. Pat. No. 5,073,373 issued Dec. 17, 1991. Bone lamellae in the shape of threads or filaments retaining low molecular weight glycerol carrier are disclosed in U.S. Pat. Nos. 5,314,476 issued May 24, 1994 and 5,507,813 issued Apr. 16, 1996 and the tissue forms described in these patents are known commercially as the GRAFTON® Putty and Flex, respectively.

U.S. Pat. No. 5,356,629 issued Oct. 18, 1994 discloses making a rigid gel in the nature of a bone cement to fill defects in bone by mixing biocompatible particles, preferably polymethylmethacrylate coated with polyhydroxyethylmethacrylate in a matrix selected from a group which lists hyaluronic acid to obtain a molded semi-solid mass which can be suitably worked for implantation into bone. The hyaluronic acid can also be utilized in monomelic form or in polymeric form preferably having a molecular weight not greater than about one million Daltons. It is noted that the nonbioabsorbable material which can be used to form the biocompatible particles can be derived from xenograft bone, homologous bone, autogenous bone as well as other materials. The bioactive substance can also be an osteogenic agent such as demineralized bone powder, morselized cancellous bone, aspirated bone marrow and other autogenous bone sources. The average size of the particles employed is preferably about 0.1 to about 3.0 mm, more preferably about 0.2 to about 1.5 mm, and most preferably about 0.3 to about 1.0 mm. It is inferentially mentioned but not taught that particles having average sizes of about 7,000 to 8,000 microns, or even as small as about 100 to 700 microns can be used.

U.S. Pat. No. 4,172,128 issued Oct. 23, 1979 discloses a demineralized bone material mixed with a carrier to reconstruct tooth or bone material by adding a mucopolysaccharide to a mineralized bone colloidal material. The composition is formed from a demineralized coarsely ground bone material, which may be derived from human bones and teeth, dissolved in a solvent forming a colloidal solution to which is added a physiologically inert polyhydroxy compound such as mucopolysaccharide or polyuronic acid in an amount which causes orientation when hydrogen ions or polyvalent metal ions are added to form a gel. The gel will be flowable at elevated temperatures above 35° C. and will solidify when brought down to body temperature. Example 25 of the patent notes that mucopolysaccharides produce pronounced ionotropic effects and that hyaluronic acid is particularly responsible for spatial cross-linking.

U.S. Pat. No. 6,030,635 issued Feb. 29, 2000 and U.S. Pat. No. 6,437,018 issued Aug. 20, 2002 are directed toward a malleable bone putty and a flowable gel composition for application to a bone defect site to promote new bone growth at the site which utilize a new bone growth inducing compound of demineralized lyophilized allograft bone powder. The bone powder has a particle size ranging from about 100 to about 850 microns and is mixed in a high molecular weight hydrogel carrier which contains a sodium phosphate saline buffer.

The use of implants for cartilage defects is much more limited. Aside from the fresh allograft implants and autologous implants, U.S. Pat. No. 6,110,209 issued Nov. 5, 1998 shows the use an autologous articular cartilage cancerous bone paste to fill arthritic defects. The surgical technique is arthroscopic and includes debriding (shaving away loose or fragmented articular cartilage), followed by morselizing the base of the arthritic defect with an awl until bleeding occurs. An osteochondral graft is then harvested from the inner rim of the intercondylar notch using a trephine. The graft is then morselized in a bone graft crusher, mixing the articular cartilage with the cancellous bone. The paste is then pushed into the defect and secured by the adhesive properties of the bleeding bone. The paste can also be mixed with a cartilage stimulating factor, a plurality of cells, or a biological glue. All patients are kept non-weight bearing for four weeks and used a continuous passive motion machine for six hours each night. Histologic appearance of the biopsies have mainly shown a mixture of fibrocartilage with hyaline cartilage.

Concerns associated with this method are harvest site morbidity and availability, similar to the mosaicplasty method. cl

SUMMARY OF THE INVENTION

A cartilage implant material in paste or gel form for repairing articular cartilage defects is composed of milled allograft cartilage pieces in a bioabsorbable carrier. Autologous chondrocyte in an amount exceeding the number naturally occurring in hyaline cartilage for a mature adult between 20 and 55 years of age may also be applied to the matrix. Additives may be applied to the mixture in order to increase chondrocyte migration and proliferation. The implant material can support the addition of a variety of chondrogenic stimulating factors including, but not limited to growth factors (FGF-2, FGF-5, IGF-1, TGF-β, BMP-2, BMP-7, PDGF, VEGF), human allogenic or autologous chondrocytes, human allogenic or autologous bone marrow cells, stem cells, demineralized bone matrix, insulin, insulin-like growth factor-1, transforming growth factor-B, interleukin-1 receptor antagonist, hepatocyte growth factor, platelet-derived growth factor, Indian hedgehog and parathyroid hormone-related peptide or bioactive glue.

The implant material is placed in the lesion area and may be sealed with a periosteum cap.

It is an object of the invention to provide an allograft implant material for joints which provides pain relief, restores normal function and will postpone or alleviate the need for prosthetic replacement.

It is also an object of the invention to provide a cartilage repair implant material which is easily placed in a defect area by the surgeon using an arthroscopic, minimally invasive technique.

It is further an object of the invention to provide an allograft implant material procedure which is applicable for both partial and full thickness lesions.

It is yet another object of the invention to provide an allograft implant material which facilitates growth of hyaline cartilage.

It is an additional object of the invention to provide implant paste and gel material formulations that satisfy surgical requirements and are made from donated human available allograft tissue, some of which would otherwise be considered waste and thrown away.

These and other objects, advantages, and novel features of the present invention will become apparent when considered with the teachings contained in the detailed disclosure along with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** shows the anatomy of a knee joint with a lesion;

FIG. **2** shows a schematic mosaicplasty as known in the prior art; and

FIG. **3** shows a schematic perspective view of cartilage defect material placed in a defect site with an exploded periosteum cap.

DESCRIPTION OF THE INVENTION

The terms "tissue" is used in the general sense herein to mean any transplantable or implantable tissue, the survivability of which is improved by the methods described herein upon implantation. In particular, the overall durability and longevity of the implant are improved, and host-immune system mediated responses, are substantially eliminated.

The terms "transplant" and "implant" are used interchangably to refer to tissue, material or cells (xenogeneic or allogeneic) which may be introduced into the body of a patient to replace or supplement the structure or function of the endogenous tissue.

The terms "autologous" and "autograft" refer to tissue or cells which originate with or are derived from the recipient, whereas the terms "allogeneic" and "allograft" refer to cells and tissue which originate with or are derived from a donor of the same species as the recipient. The terms "xenogeneic" and "xenograft" refer to cells or tissue which originates with or is derived from a species other than that of the recipient.

The term "gel" refers to a mixture of minced or milled pretreated allograft cartilage in a biocomposite carrier having a viscosity which is less than and is less rigid than a mixture of minced or milled pretreated allograft cartilage in a biocompatible carrier referred to by the terms "putty" or "paste" and contains less cartilage by weight than putty or paste.

The present invention is directed towards a cartilage repair material and method of treatment. The preferred embodiment and best mode of the invention is shown in FIG. **3**. In the production of the invention, allograft hyaline cartilage is lyophilized reducing its water content and milled for ease in application.

After washes with sterile de-ionized (DI) water, the cartilage material was frozen at −20° to −100° C. preferably −70° C. and lyophilized to reduce the water content within the range of about 0.1% to about 8.0%. The cartilage is frozen with liquid nitrogen and ground into particles.

A lesion or defect is removed by cutting a bore **50** or trimming a lesion in the implant area **100** and filling the bore **50** or lesion area with a milled cartilage mixture **20** of paste or gel consisting together with a biological carrier such as hyaluronic acid and its derivatives, gelatin, collagen, chitosan, alginate, buffered PBS, Dextran, or polymers and one or more additives namely chondrogenic stimulating factors including, but not limited to growth factors (FGF-2, FGF-5, IGF-1, TGF-β, BMP-2, BMP-7, PDGF, VEGF), human allogenic or autologous chondrocytes, human allogenic cells, human allogenic or autologous bone marrow cells, human allogenic or autologous stem cells, demineralized bone matrix, insulin, insulin-like growth factor-1, interleukin-1 receptor antagonist, hepatocyte growth factor, platelet-derived growth factor, Indian hedgehog and parathyroid hormone-related peptide.

Suitable organic glue material can be used to keep the viscous cartilage mixture **20** fixed in place in the implant area or to affix a periosteal cap **30** in place over the surrounding hyaline cartilage area **100**. Suitable organic glue material can be found commercially, such as for example; TISSEEL® or TISSUCOL®) (fibrin based adhesive; Immuno AG, Austria), Adhesive Protein (Sigma Chemical, USA), and Dow Corning Medical Adhesive B (Dow Corning, USA).

EXAMPLE 1

A matrix of minced cartilage putty consisting of minced or milled allograft articular cartilage which has been lyophilized so that its water content ranges from 0.1% to 8.0% with a cartilage content ranging from 25% to 50% by weight is mixed with a carrier of sodium hyaluronate solution (HA) (molecular weight ranging from 7.0×10^5 to 1.2×10^6) or any other bioabsorbable carrier such as hyaluronic acid and its derivatives, gelatin, collagen, chitosan, alginate, buffered PBS, Dextran, or polymers, the carrier ranging from 75% to 50% by weight. The cartilage is milled to a size ranging from 0.01 mm to 1 mm. In gel form, the minced cartilage which

has been lyophilized so that its water content ranges from 0.1% to 8.0% ranging from 15% to 30% by weight and the carrier ranges from 85% to 70% by weight. The particle size of the cartilage when milled is less than or equal to 1 mm dry in the previously stated range. The cartilage pieces can be processed to varying particle sizes and the HA or other carrier can have different viscosities depending on the desired consistency of the putty or paste. This cartilage matrix can be deposited into the cartilage defect arthroscopically and fit into the defect where it is held in place by it's own viscosity, mixed with fibrin glue or covered with a periosteal or perichondrial flap, then sealed with biological glue. As with the first two matrices, this matrix can support the previously mentioned chondrogenic factors.

EXAMPLE 2

A matrix of minced cartilage putty consisting of minced or milled allograft cartilage which has been lyophilized so that its water content ranges from 0.1% to 8.0% ranging from 25% to 50% by weight is mixed with a carrier of sodium hyaluronate solution (HA) (7.0×10^5 to 1.2×10^6) or any other bioabsorbable carrier such as hyaluronic acid and its derivatives, gelatin, collagen, chitosan, alginate, buffered PBS, Dextran, or polymers ranging from 75% to 50% by weight. In a gel form, the minced cartilage which has been lyophilized so that its water content ranges from 0.01% to 8.0% ranging from 15% to 30% by weight and the carrier ranges from 85% to 70% by weight. The particle size of the cartilage is less than or equal to 1 mm dry ranging from 0.01 mm to 1 mm. The cartilage pieces can be processed to varying particle sizes and the HA or carrier can have different viscosities depending on the desired consistency of the putty or paste. Autologous or allogenic cells which have been grown outside the patient are inserted by syringe into the matrix before, during or after deposit of the cartilage matrix into the defect area. Such cells include allogenic or autologous bone marrow cells, stem cells and chondrocyte cells. The cellular density of the cells preferably ranges from about 1×10^8 to 5×10^8 or from about 100 million to about 500 million cells per cc of putty or gel mixture. This composite material can be injected into the cartilage defect arthroscopically and fit into the defect where it is held in place by it's own viscosity, or covered with a periosteal or perichondrial flap, then sealed with biological glue. As with the first matrix, this matrix can support the previously mentioned chondrogenic factors.

The operation of placing the cartilage composition in a cartilage defect, comprises (a) cutting a patient's tissue at a site of a cartilage defect to remove the diseased area of cartilage; (b) placing a mixture of milled allograft cartilage in a bioabsorbable carrier in the defect area; and (c) placing a periosteal cover over the mixture of the inserted milled allograft cartilage in a bioabsorbable carrier to contain the mixture in the defect area for a predetermined period of time to promote cartilage growth at the defect site. Alternate steps include the addition of growth factors, chondrocytes, bone marrow cells and stem cells.

The principles, preferred embodiments and modes of operation of the present invention have been described in the foregoing specification. However, the invention should not be construed as limited to the particular embodiments which have been described above. Instead, the embodiments described here should be regarded as illustrative rather than restrictive.

What we claim is:

1. A **[**sterile allograft**]** cartilage defect **[**implant**]** *repair* material for use in human beings, comprising *a mixture including lyophilized, freeze*-milled allograft cartilage pieces **[**sized less**]** *having a size not greater* than 1 mm and *a bioabsorbable carrier, said cartilage pieces being formed from allograft cartilage that has been* lyophilized so **[**that their**]** *as to reduce its* water content **[**ranges from**]** *to an amount within the range of from* about 0.1% to about 8.0% **[**in a bioabsorbable carrier**]** *by weight*.

[2. A sterile allograft cartilage defect implant material as claimed in claim **1** wherein said milled cartilage ranges from about 25% to about 50% by weight and said carrier ranges from about 75% to about 50% by weight.**]**

[3. A sterile allograft cartilage defect implant material as claimed in claim **1** wherein said milled cartilage ranges from about 15% to about 30% by weight with the carrier ranging from about 85% to about 70% by weight.**]**

4. A **[**sterile allograft**]** cartilage defect **[**implant**]** *repair* material as claimed in claim **1**, wherein said *bioabsorbable* carrier is *selected from the group consisting of* sodium hyaluronate and **[**its derivatives**]** hyaluronic acid.

5. A **[**sterile allograft**]** cartilage defect **[**implant**]** *repair* material as claimed in claim **1**, wherein said **[**implant material**]** *mixture* includes a protein glue.

6. A **[**sterile allograft**]** cartilage defect **[**implant**]** *repair* material as claimed in claim **1**, wherein said **[**implant material**]** *mixture* includes **[**the addition of**]** autologous chondrocytes **[**to achieve a concentration exceeding the concentration of chondrocytes naturally occurring in the patient**]** *at a concentration greater than the concentration of chondrocytes that are naturally present in hyaline cartilage of a human being having an age in the range of from 20 years to 55 years*.

7. A **[**sterile allograft**]** cartilage defect **[**implant**]** *repair* material as claimed in claim **1**, wherein said **[**milled**]** *allograft* cartilage **[**is**]** *pieces include* hyaline cartilage.

8. A **[**sterile allograft**]** cartilage defect **[**implant**]** *repair* material as claimed in claim **1**, wherein said **[**milled**]** *allograft* cartilage **[**is fibrosus cartilage**]** *pieces include fibrocartilage*.

9. A **[**sterile allograft**]** cartilage defect **[**implant**]** *repair* material as claimed in claim **1**, wherein said **[**milled**]** *allograft* cartilage **[**is**]** *pieces include* hyaline and **[**fibrosus cartilage**]** *fibrocartilage*.

10. A **[**sterile allograft**]** cartilage defect **[**implant**]** *repair* material *as* claimed in claim **1**, **[**including**]** *wherein said mixture includes* an additive **[**to said implant material consisting of one or more of a**]** *selected from the* group consisting of *a* growth **[**factors**]** *factor*, human allogenic cells, human allogenic bone marrow cells, human autologous bone marrow cells, human allogenic stem cells, human autologous stem cells, *a* human demineralized bone matrix, **[**and**]** insulin, *insulin-like growth factor-1, an interleukin-1, receptor agonist, a hepatocyte growth factor, a platelet-derived growth factor, Indian hedgehog, and a parathryroid hormone-related peptide*.

11. A **[**sterile**]** cartilage *defect* repair material as claimed in claim **10**, wherein said growth **[**factors are one or more of a**]** *factor is selected from the* group consisting of FGF-2, FGF-5, IGF-1, TGF-β, BMP-2, BMP-7, PDGF, *and* VEGF.

12. A **[**sterile allograft**]** cartilage defect **[**implant**]** *repair* material as claimed in claim **1**, wherein said *bioabsorbable* carrier **[**comprises one or more bioabsorbable carriers taken**]** *is selected* from **[**a**]** *the* group consisting of sodium hyaluronate, hyaluronic acid **[**and its derivatives**]**, gelatin, collagen, chitosan, alginate, buffered PBS, Dextran, **[**or**]** *and* polymers.

13. A **[**sterile allograft**]** cartilage defect **[**implant**]** *repair* material *for use in human beings,* comprising *a mixture*

including lyophilized, freeze-milled allograft articular cartilage pieces ranging from 0.01 mm to 1.0 mm in size **[**in**]**, a bioabsorbable carrier **[**taken**]** *selected* from **[**a**]** *the* group consisting of sodium hyaluronate, *hyaluronic acid,* gelatin, collagen, chitosan, alginate, buffered PBS, Dextran, **[**or**]** *and* polymers, and allogenic chondrocytes **[**in an amount exceeding the natural occurrence of same in articular cartilage**]** *at a concentration greater than the concentration of chondrocytes that are naturally present in hyaline cartilage of a human being having an age in the range of from 20 years and 55 years*.

14. A **[**sterile**]** cartilage defect **[**implant**]** *repair* material as claimed in claim **13**, wherein said allograft articular cartilage **[**is**]** *pieces include* hyaline cartilage.

15. A **[**sterile allograft**]** cartilage defect **[**implant**]** *repair* material as claimed in claim **13**, wherein said **[**milled**]** *allograft articular* cartilage **[**is fibrous cartilage**]** *pieces include fibrocartilage*.

16. A **[**sterile allograft**]** cartilage defect **[**implant**]** *repair* material as claimed in claim **13**, wherein said **[**milled**]** *allograft articular* cartilage **[**is**]** *pieces include* hyaline *cartilage* and **[**fibrous cartilage**]** *fibrocartilage*.

17. A **[**sterile**]** cartilage *defect* repair material as claimed in claim **13** **[**wherein said implant material includes**]**, *further comprising* an additive **[**consisting of one or more of a**]** *selected from the* group consisting of *a* growth **[**factors**]** *factor*, human allogenic cells, human allogenic bone marrow cells, human autologous bone marrow cells, human allogenic stem cells, human autologous stem cells, demineralized bone matrix, **[**and**]** insulin, *insulin-like growth factor-1, interleukin-1 receptor agonist, hepatocyte growth factor, platelet-derived growth factor, Indian hedgehog, and parathyroid hormone-related peptide*.

18. A **[**sterile**]** cartilage *defect* repair material as claimed in claim **17**, wherein said growth **[**factors are one or more of a**]** *factor is selected from the* group consisting of FGF-2, FGF-5, IGF-1, TGF-β, BMP-2, BMP-7, PDGF, *and* VEGF.

[19. A sterile cartilage defect implant material as claimed in claim **13** wherein said milled cartilage ranges from about 25% to about 50% by weight and said carrier ranges from about 75% to about 50% by weight.**]**

[20. A sterile cartilage defect implant material as claimed in claim **13** wherein said milled cartilage ranges from about 15% to about 30% by weight with the carrier ranging from about 85% to about 70% by weight.**]**

21. A **[**sterile allograft**]** cartilage defect **[**implant**]** *repair* material *for use in human beings,* comprising lyophilized, *freeze*-milled allograft articular cartilage pieces ranging from 0.01 mm to 1.0 mm in size **[**in**]**, a bioabsorbable carrier **[**taken**]** *selected* from **[**a**]** *the* group consisting of sodium hyaluronate, hyaluronic acid **[**and its derivatives**]**, gelatin, collagen, chitosan, alginate, buffered PBS, Dextran **[**or**]**, *and* polymers, and autologous bone marrow cells **[**in an amount exceeding the natural occurrence of same in a patient being treated**]** *at a concentration greater than the concentration of bone marrow cells that are naturally present in hyaline cartilage of a human being having an age in the range of from 20 years to 55 years*.

22. A **[**sterile**]** cartilage defect repair material as claimed in claim **21** **[**including**]**, *further comprising* an additive **[**in said implant material which consists of one or more of a**]** *selected from the* group consisting of *a* growth **[**factors**]** *factor*, human allogenic cells, autologous chondrocytes, demineralized bone matrix, **[**and**]** insulin, *insulin-like growth factor-1, an interleukin-1 receptor agonist, a hepatocyte growth factor, a platelet-derived growth factor, Indian hedgehog, and a parathyroid hormone-related peptide*.

23. A **[**sterile**]** cartilage *defect* repair material as claimed in claim **22**, wherein said growth **[**factors are one or more of a**]** *factor is selected from the* group consisting of FGF-2, FGF-5, IGF-1, TGF-β, BMP-2, BMP-7, PDGF, *and* VEGF.

24. A **[**sterile allograft**]** cartilage defect **[**implant**]** *repair* material as claimed in claim **21**, wherein said bioabsorbable carrier **[**consists**]** *is selected from the group consisting* of sodium hyaluronate**[**,**]** *and* hyaluronic acid **[**and its derivatives**]**.

25. A **[**sterile**]** cartilage defect *repair* material as claimed in claim **21**; wherein said **[**lyophilized**]** *allograft articular* cartilage pieces **[**have ranging from**]** *are formed from allograft articular cartilage that has been lyophilized so as to reduce its water content to the range of* about 0.1% to *about* 8.0%.

26. A **[**sterile allograft**]** cartilage defect **[**implant**]** *repair* material as claimed in claim **21**, wherein said allograft articular cartilage **[**is**]** *pieces include* hyaline cartilage.

27. A **[**sterile allograft**]** cartilage defect **[**implant**]** *repair* material as claimed in claim **21**, wherein said **[**milled**]** *allograft articular* cartilage **[**is fibrous cartilage**]** *pieces include fibrocartilage*.

28. A **[**sterile allograft**]** cartilage defect **[**implant**]** *repair* material as claimed in claim **21**, wherein said **[**milled**]** *allograft articular* cartilage **[**is**]** *pieces include* hyaline *cartilage* and **[**fibrous cartilage**]** *fibrocartilage*.

29. A **[**sterile allograft**]** cartilage defect **[**implant**]** *repair* material as claimed in claim **21**, wherein said **[**milled**]** *allograft articular* cartilage **[**ranges**]** *pieces are present in said material at an amount in the range of* from about 25% to about 50% by weight and said *bioabsorbable* carrier **[**ranges**]** *is present in said material at an amount in the range of* from about **[**75%**]** *50%* to about **[**50%**]** *75%* by weight.

30. A **[**sterile allograft**]** cartilage defect **[**implant**]** *repair* material as claimed in claim **21**, wherein said **[**milled**]** *allograft articular* cartilage **[**ranges**]** *pieces are present in said material in an amount in the range of* from about 15% to about 30% by weight **[**with the**]** *and said bioabsorbable* carrier **[**ranging**]** *is present in said material in an amount in the range of* from about **[**85%**]** *70%* to about **[**70%**]** *85%* by weight.

[31. A sterile cartilage defect implant material comprising lyophilized milled allograft articular cartilage pieces ranging from 0.01 mm to 1.0 mm in size in a bioabsorbable carrier taken from a group consisting of sodium hyaluronate, hyaluronic acid and its derivatives, gelatin, collagen, chitosan, alginate, buffered PBS, Dextran or polymers and autologous stem cells in an amount exceeding the natural occurrence of same in a patient being treated.**]**

32. A method of placing a cartilage defect *repair* material in a cartilage defect *site in a human being*, **[**said**]** *the* cartilage **[**defect**]** *repair* material **[**comprising**]** *having a mixture including lyophilized freeze*-milled allograft articular cartilage **[**which has been lyophilized and mixed in**]** *pieces and* a bioabsorbable carrier, *said method* comprising the steps of:

(a) cutting a patient's tissue **[**at a site of a cartilage defect**]** to remove **[**a**]** diseased **[**area of**]** cartilage *from the cartilage defect site*;

(b) adding **[**autologous**]** cells to **[**said**]** *the* mixture **[**of milled allograft cartilage in a bioabsorbable carrier**]**;

(c) placing **[**a**]** *the* mixture **[**of milled allograft cartilage**]** with *the* added **[**autologous**]** cells **[**in a bioabsorbable carrier in**]** *into* the cartilage defect **[**area where cartilage has been removed**]** *site*; and

(d) placing a cover over the mixture **[**of milled allograft cartilage in a bioabsorbable carrier**]** *and the added cells so as* to contain the mixture *and the added cells* in *the* cartilage defect site **[**for a predetermined period of time**]**.

33. The method of claim 32, [wherein] *further comprising the step of adding* growth factors [are added] to [said] *the* mixture.

34. The method of claim 32, wherein said [autologous] cells [are] *include* chondrocytes.

35. The method of claim 32, wherein said [autologous] cells [are] *include* bone marrow cells.

36. The method of claim 32, wherein said [autologous] cells [are] *include* stem cells.

37. A [sterile allograft] cartilage defect [implant] *repair* material *for use in a human being,* comprising *a mixture including* lyophilized, *freeze*-milled allograft articular cartilage pieces ranging from 0.01 mm to 1.0 mm in size [in], a bioabsorbable carrier [taken] *selected* from [a] *the* group consisting of sodium hyaluronate, hyaluronic acid [and its derivatives], and chitosan, and autologous chondrocytes [in an amount exceeding the natural occurrence of same in articular cartilage] *at a concentration greater than the concentration of chondrocytes that are naturally present in hyaline cartilage of a human being having an age in the range of from 20 years and 55 years,* wherein said [milled] *allograft articular* cartilage [ranges] *pieces are present in said mixture at an amount within the range of* from about 25% to about 50% by weight and said bioabsorbable carrier [ranges] *is present in said mixture at an amount within the range of* from about [75%] *50%* to about [50%] *75%* by weight.

38. A [sterile allograft] cartilage defect [implant] *repair* material *for use in a human being,* comprising *a mixture including* lyophilized, *freeze*-milled allograft articular cartilage pieces ranging from 0.01 mm to 1.0 mm in size [in], a bioabsorbable carrier [taken] *selected* from [a] *the* group consisting of gelatin, collagen, and alginate, and autologous chondrocytes [in an amount exceeding the natural occurrence of same in articular cartilage] *at a concentration greater than the concentration of chondrocytes that are naturally present in hyaline cartilage of a human being having an age in the range of from 20 years and 55 years,* wherein said [milled] *allograft articular* cartilage [ranges] *pieces are present in said mixture at an amount within the range of* from about 25% to about 50% by weight and said bioabsorbable carrier [ranges] *is present in said mixture at an amount within the range of* from about [75%] *50%* to about [50%] *75%* by weight.

39. A [sterile allograft] cartilage defect [implant] *repair* material *for use in a human being,* comprising *a mixture including* lyophilized, *freeze*-milled allograft articular cartilage pieces ranging from 0.01 mm to 1.0 mm in size [in], a bioabsorbable carrier [taken] *selected* from [a] *the* group consisting of buffered PBS, Dextran [or], *and* polymers, and autologous chondrocytes [in an amount exceeding the natural occurrence of same in articular cartilage] *at a concentration greater than the concentration of chondrocytes that are naturally present in hyaline cartilage of a human being having an age in the range of from 20 years and 55 years*, wherein said [milled] *allograft articular* cartilage [ranges] *pieces are present in said mixture at an amount within the range of* from about 25% to about 50% by weight and said bioabsorbable carrier [ranges] *is present in said mixture at an amount within the range of* from about [75%] *50%* to about [50%] *75%* by weight.

40. A cartilage defect repair material as claimed in claim 1, wherein said cartilage pieces are present in said mixture at an amount within the range of from about 25% to about 50% by weight, and said bioabsorbable carrier is present in said mixture at an amount within the range of from about 50% to about 75% by weight.

41. A cartilage defect repair material as claimed in claim 1, wherein said cartilage pieces are present in said mixture at an amount within the range of from about 15% to about 30% by weight, and said bioabsorbable carrier is present in said mixture at an amount within the range of from about 70% to about 85% by weight.

42. A cartilage defect repair material as claimed in claim 1, wherein said lyophilized. freeze-milled allograft cartilage pieces lack cell viability.

43. A cartilage defect repair material as claimed in claim 1, wherein said cartilage defect repair material is free of bone pieces.

44. A cartilage defect repair material as claimed in claim 1, wherein said lyophilized, freeze-milled allograft cartilage pieces are formed by a process including the steps of harvesting a donor tissue consisting essentially of articular cartilage, lyophilizing said donor tissue, and freeze-milling said donor tissue.

45. A cartilage defect repair material as claimed in claim 1, wherein said lyophilized, freeze-milled allograft cartilage pieces are formed by milling frozen allograft articular cartilage.

46. A cartilage defect repair material as claimed in claim 1, wherein said lyophilized, freeze-milled cartilage pieces are formed by freezing allograft cartilage with liquid nitrogen and milling the frozen cartilage.

47. A cartilage defect repair material as claimed in claim 1, wherein said cartilage defect repair material is free of added chondrocytes.

48. A cartilage defect repair material as claimed in claim 1, wherein said lyophilized, freeze-milled allograft cartilage pieces have an ability to promote the growth of new articular cartilage in the cartilage defect.

49. A cartilage defect repair material as claimed in claim 13, wherein said mixture includes a protein glue.

50. A cartilage defect repair material as claimed in claim 13, wherein said allograft articular cartilage pieces are formed from allograft articular cartilage that has been lyophilized so as to reduce its water content to the range of from about 0.1% to about 8.0% by weight.

51. A cartilage defect repair material as claimed in claim 13, wherein said cartilage pieces are present in said mixture at an amount within the range of from about 25% to about 50% by weight, and said bioabsorbable carrier is present in said mixture at an amount within the range of from about 50% to about 75% by weight.

52. A cartilage defect repair material as claimed in claim 13, wherein said cartilage pieces are present in said mixture at an amount within the range of from about 15% to about 30% by weight, and said bioabsorbable carrier is present in said mixture at an amount within the range of from about 70% to about 85% by weight.

53. A cartilage defect repair material as claimed in claim 21, further comprising a protein glue.

54. The method of claim 32, further comprising the step of fixing the mixture in the cartilage defect site with an organic glue.

55. The method of claim 32, further comprising the step of keeping the cover over the mixture for a predetermined period of time that is sufficient to promote cartilage growth at the cartilage defect site.

56. The method of claim 32, wherein said cover is a periosteal flap.

57. The method of claim 32, wherein said cover is a perichondrial flap.

58. The method of claim 32, wherein, in said step (b), the cells are selected from the group consisting of chondrocytes, bone marrow cells and stem cells, and the cells are added so as to achieve a concentration greater than the concentration

of corresponding cells that are naturally present in hyaline cartilage of a human being having an age in the range of from 20 years and 55 years.

59. A cartilage defect repair material for use in human beings, comprising lyophilized, freeze-milled allograft cartilage pieces having a size not greater than 1 mm, wherein said cartilage pieces are included in a mixture that also includes a bioabsorbable carrier, said cartilage pieces being present in said mixture at an amount within the range of from about 25% to about 50% by weight, and said bioabsorbable carrier being present in said mixture at an amount within the range of from about 50% to about 75% by weight.

60. A cartilage defect repair material as claimed in claim 59, wherein said cartilage pieces are formed from allograft cartilage that has been lyophilized so as to reduce its water content to an amount within the range of from about 0.1% to about 8.0% by weight.

61. A cartilage defect repair material as claimed in claim 59, wherein said size ranges from 0.01 mm to 1.0 mm.

62. A cartilage defect repair material as claimed in claim 59, wherein said material is free of added chondrocytes.

63. A cartilage defect repair material as claimed in claim 59, wherein said cartilage pieces are formed by freezing allograft cartilage with liquid nitrogen and milling the frozen cartilage.

64. A cartilage defect repair material as claimed in claim 59, wherein said cartilage pieces are formed by freeze-milling allograft cartilage subsequent to lyophilization.

65. A cartilage defect repair material for use in human beings, comprising lyophilized, freeze-milled allograft cartilage pieces having a size not greater than 1 mm, wherein said cartilage pieces are included in a mixture that also includes a bioabsorbable carrier, said cartilage pieces being present in said mixture at an amount within the range of from about 15% to about 30% by weight, and said bioabsorbable carrier being present in said mixture at an amount within the range of from about 70% to about 85% by weight.

66. A cartilage defect repair material as claimed in claim 65, wherein said cartilage pieces are formed from allograft cartilage that has been lyophilized so as to reduce its water content to an amount within the range of from about 0.1% to about 8.0% by weight.

67. A cartilage defect repair material as claimed in claim 65, wherein said size ranges from 0.01 mm to 1.0 mm.

68. A cartilage defect repair material as claimed in claim 65, wherein said material is free of added chondrocytes.

69. A cartilage defect repair material as claimed in claim 65, wherein said cartilage pieces are formed by freezing allograft cartilage with liquid nitrogen and milling the frozen cartilage.

70. A cartilage defect repair material as claimed in claim 65, wherein said cartilage pieces are formed by freeze-milling allograft cartilage subsequent to lyophilization.

71. A method of repairing a cartilage defect in a human being, comprising the step of placing in a defect site lyophilized, freeze-milled allograft cartilage pieces having a size not greater than 1 mm.

72. A method as claimed in claim 71, wherein the cartilage pieces have a water content ranging from about 0.1% to about 8.0% by weight prior to their placement in the defect site.

73. A method as claimed in claim 71, wherein the cartilage pieces are formed from allograft cartilage which has been lyophilized so as to reduce its water content to an amount within the range of from about 0.1% to about 8.0% by weight.

74. A method as claimed in claim 71, wherein the size ranges from 0.01 mm to 1.0 mm.

75. A method as claimed in claim 71, wherein the cartilage pieces are formed by freezing allograft cartilage with liquid nitrogen and milling the frozen cartilage.

76. A method as claimed in claim 71, wherein the cartilage pieces are formed by freeze-milling allograft cartilage subsequent to lyophilization of the allograft cartilage.

77. A method as claimed in claim 71, wherein the defect site includes a defect in articular cartilage.

78. A method as claimed in claim 77, wherein the cartilage pieces have an ability to promote the growth of new articular cartilage in the articular cartilage defect.

79. A method as claimed in claim 71, wherein the lyophilized, freeze-milled allograft cartilage pieces consist essentially of articular cartilage.

80. A method as claimed in claim 71, wherein the lyophilized, freeze-milled allograft cartilage pieces lack cell viability.

81. A method as claimed in claim 71, comprising the further steps of harvesting a donor tissue consisting essentially of articular cartilage, lyophilizing said donor tissue, and freeze-milling said donor tissue.

82. A method as claimed in claim 71, comprising the further step of forming the lyophilized, freeze-milled allograft cartilage pieces by a process including the step of milling frozen allograft articular cartilage.

83. A method as claimed in claim 71, wherein the lyophilized, freeze-milled allograft cartilage pieces are free of added chondrocytes.

* * * * *