



US007368502B2

(12) **United States Patent**
Calabro et al.

(10) **Patent No.:** **US 7,368,502 B2**
(45) **Date of Patent:** **May 6, 2008**

(54) **HYDROXYPHENYL CROSS-LINKED
MACROMOLECULAR NETWORK AND
APPLICATIONS THEREOF**

FOREIGN PATENT DOCUMENTS

EP 0 516026 A1 12/1992

(75) Inventors: **Anthony Calabro**, Cleveland Heights,
OH (US); **Richard A. Gross**, Plainview,
NY (US); **Aniq B. Darr**, Shaker
Heights, OH (US)

(Continued)

OTHER PUBLICATIONS

(73) Assignee: **The Cleveland Clinic Foundation**,
Cleveland, OH (US)

Blumenkrantz, N. and Asboe-Hansen, G. (1973) New method for
quantitative determination of uronic acids. *Anal. Biochem.* 54,
484-489.

(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 441 days.

(Continued)

Primary Examiner—Irina S Zemel

(74) *Attorney, Agent, or Firm*—Pearne & Gordon LLP

(21) Appl. No.: **11/198,803**

(57) **ABSTRACT**

(22) Filed: **Aug. 5, 2005**

(65) **Prior Publication Data**

US 2005/0265959 A1 Dec. 1, 2005

Related U.S. Application Data

(62) Division of application No. 10/753,779, filed on Jan.
8, 2004, now Pat. No. 6,982,298.

(51) **Int. Cl.**

C08L 89/00 (2006.01)

C08G 63/48 (2006.01)

(52) **U.S. Cl.** **525/54.1**; 525/54.2; 525/326.1;
525/420; 525/540; 527/600; 521/189; 521/180

(58) **Field of Classification Search** 525/54.1,
525/54.2, 326.1, 420, 540; 521/180, 189;
527/600

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,277,582 A 7/1981 Mueller et al.

4,350,629 A 9/1982 Yannas et al.

A dihydroxyphenyl cross-linked macromolecular network is provided that is useful in artificial tissue and tissue engineering applications, such as artificial or synthetic cartilage. The network is made by first providing a polyamine or polycarboxylate macromolecule (having a plurality of amine or carboxylic acid groups respectively attached along the length of the molecule), reacting this macromolecule with a hydroxyphenyl compound having a free carboxylic acid group in the case of a polyamine or a free primary amine group in the case of a polycarboxylate, and substituting the hydroxyphenyl compound onto the macromolecule via a carbodiimide-mediated reaction pathway to provide a hydroxyphenyl-substituted macromolecule. This macromolecule is then linked to other such macromolecules via an enzyme catalyzed dimerization reaction between two hydroxyphenyl groups attached respectively to different macromolecules under metabolic conditions of temperature and pH. In a preferred embodiment, the macromolecular network is made up of tyramine-substituted hyaluronan molecules that are linked by dityramine bonds to provide a stable, coherent hydrogel with desired physical properties. A method of preparing such a network is also provided.

(Continued)

27 Claims, 4 Drawing Sheets

