anate. The isothiocyanates will react with the amines to form a chemically crosslinked gel. Aldehyde reactions with amines, e.g., with polyethylene glycol dialdehyde also may be utilized. A hydroxylated water soluble polymer also may be utilized.

Alternatively, polymers may be utilized which include substituents which are crosslinked by a radical reaction upon contact with a radical initiator. For example, polymers including ethylenically unsaturated groups which can be photochemically crosslinked may be utilized, as disclosed in WO 93/17669, the disclosure of which is incorporated herein by reference. In this embodiment, water soluble macromers that include at least one water soluble region, a biodegradable region, and at least two free radical-polymerizable regions, are provided. The macromers are polymerized by exposure of the polymerizable regions to free radicals generated, for example, by photosensitive chemicals and or light. Examples of these macromers are PEG-oligolactyl-acrylates, wherein the acrylate groups are polymerized using radical initiating systems, such as an eosin dye, or by brief exposure to ultraviolet or visible light. Additionally, water soluble polymers which include cinnamoyl groups which may be photochemically crosslinked may be utilized, as disclosed in Matsuda et al., *ASAID Trans.,* 38–157 (1992).

Density Modifying Agents

Although described herein particularly with reference to polymers which increase the viscosity and/or density of the material to be injected into the tissue to be treated, other materials could also be used which are not polymers. Many agents which increase viscosity or density are routinely used, especially in the food and medical industry. Generally, these include proteins such as albumin, sugars such as dextran, glucose and fructose, and strarches, although these are technically polymers. As used herein, the term "polymers" encompasses the addition of monomers or single unit material that function to increase the viscosity and/or density of the solution to be injected into the tissue to be treated.

Polysaccharides that are very viscous liquids or are thixotropic, and form a gel over time by the slow evolution of structure, are especially useful. For example, hyaluronic acid, which forms an injectable gel with a consistency like a hair gel, may be utilized. Modified hyaluronic acid derivatives are particularly useful. As used herein, the term "modified hyaluronic acids" refers to chemically modified hyaluronic acids. Modified hyaluronic acids may be designed and synthesized with preselected chemical modifications to adjust the rate and degree of crosslinking and biodegradation. For example, modified hyaluronic acids may be designed and synthesized which are esterified with a relatively hydrophobic group such as propionic acid or benzylic acid to render the polymer more hydrophobic and gel-forming, or which are grafted with amines to promote electrostatic self-assembly. Modified hyaluronic acids thus may be synthesized which are injectable, in that they flow under stress, but maintain a gel-like structure when not under stress. Hyaluronic acid and hyaluronic derivatives are available from Genzyme, Cambridge, Mass. and Fidia, Italy.

Other materials that are dense and/or viscous include many of the lipids and sterols such as cholesterol, oils and fats.

Cell Suspensions

Preferably the polymer or density modifying agent is dissolved in an aqueous solution, preferably a 0.1 M potassium phosphate solution, at physiological pH, to a concentration yielding the desired density, for example, for alginate, of between 0.5 to 2% by weight, preferably 1%, alginate. The isolated cells are suspended in the polymer solution to a concentration of between 1 and 100 million cells/ml, most preferably approximately 100 million cells/ml. In a preferred embodiment, the polymer is fibrinogen and the cells are added to one ml of commercially available thrombin to a concentration of 100 million cells, then added to an equivalent volume of fibrinogen for injection into the tumor.

Combinations of materials increasing viscosity and density, as described above, may also be utilized.

Additives

A variety of materials can be added to the polymer-cell solution. Examples of useful materials include proteins, polysaccharides, nucleic acids, vitamins and metals or ions (calcium, sodium and potassium), and synthetic organic molecules. Examples include enzymes such as collagenase inhibitors, hemostatic agents such as thrombin, fibrinogen or calcium ions, growth factors, angiogenic factors and other growth effector molecules, bacteriostatic or bacteriocidal factors, antiinflammatories, anti-angiogenic agents, and vitamins. Growth effector molecules, as used herein, refer to molecules that bind to cell surface receptors and regulate the growth, replication or differentiation of target cells or tissue. Preferred growth effector molecules are growth factors and extracellular matrix molecules. Examples of growth factors include epidermal growth factor (EGF), platelet-derived growth factor (PDGF), transforming growth factors (TGFá, TGFâ), hepatocyte growth factor, heparin binding factor, insulin-like growth factor I or II, fibroblast growth factor (FGF), VEGF, LPA, erythropoietin, nerve growth factor, bone morphogenic proteins, muscle morphogenic proteins, and other factors known to those of skill in the art. Additional growth factors are described in "Peptide Growth Factors and Their Receptors I" M. B. Sporn and A. B. Roberts, eds. (Springer-Verlag, New York, 1990), for example, the teachings of which are incorporated by reference herein. Growth factors which are preferred when the material to be injected is fibroblasts, especially skin fibroblasts, are EGF and FGF. Many growth factors are also available commercially from vendors, such as Sigma Chemical Co. of St. Louis, Mo., Collaborative Research, Genzyme, Boehringer, R&D Systems, and GIBCO, in both natural and recombinant forms. Examples of extracellular matrix molecules include fibronectin, laminin, collagens, and proteoglycans. Other extracellular matrix molecules are described in Kleinman et al. (1987) or are known to those skilled in the art. Other growth effector molecules include cytokines, such as the interleukins and GM-colony stimulating factor, and hormones, such as insulin. These are also described in the literature and are commercially available. Collagenase inhibitors, including tissue inhibitor metalloproteinase (TIMP), may also be useful as growth effector molecules. Examples of hemostatic agents include thrombin, Factor Xa, fibrinogen, and calcium ions, typically in the form of calcium chloride or calcium gluconate. Vasoconstrictive agents such as epinephrine can also be used to contract blood vessels and thereby decrease bleeding. Bacteriostatic and bacteriocidal agents include antibiotics and other compounds used for preventing or treating infection in wounds.

The bioactive agents are typically incorporated in a range of nanograms to micrograms in a volume of 0.1 ml, although they can also be applied in dry form, as a paste or suspension.