

## COMPOSITIONS AND METHODS FOR PREVENTING ADHESION FORMATION

This is a continuation of Ser. No. 07/789,231 filed Nov. 7, 1991, now abandoned.

### BACKGROUND OF THE INVENTION

The present invention relates to the medical arts. In particular, the present invention is directed to compositions and methods for use in preventing the formation of postoperative adhesions.

Adhesion formation, in particular following peritoneal surgery, is a major source of postoperative morbidity and mortality. Appendectomy and gynecologic surgery are the most frequent surgical procedures implicated in clinically significant adhesion formation. The most serious complication of intraperitoneal adhesions is intestinal obstruction; in addition, adhesions are associated with chronic or recurrent pelvic pain and infertility in females.

The pathogenesis of adhesion formation is complex and not entirely understood. The first step is believed to involve excess fibrin deposition to form a scaffold. Organization of the fibrin scaffold by cellular elements, including fibroblasts and mesothelial cells, then follows.

Various approaches for the prevention of adhesion formation have been actively explored. In general, the treatments fall into three categories: prevention of fibrin deposition in the peritoneal exudate; reduction of local tissue inflammation; and removal of fibrin deposits.

Therapeutic attempts to prevent fibrin deposition include peritoneal lavages to dilute or wash away fibrinous exudate, surgical techniques to minimize tissue ischemia and introduction of barriers to limit apposition of healing serosal surfaces. Although the use of agents affecting coagulation of the fibrinous fluid has also been proposed, results obtained to date suggest that the use of procoagulants in areas of substantial bleeding may actually promote adhesion formation.

Physical barriers have been used in attempts to prevent adhesion formation by limiting tissue apposition during the critical period of peritoneal healing, thereby minimizing the development of fibrin matrix between tissue surfaces. Barrier agents which have been employed include both mechanical barriers and viscous solutions. Mixed results have been obtained using a barrier comprising a thin sheet of expanded polytetrafluoro-ethylene; in any event, such a membrane is less than ideal, as it must be sutured into place and is nonabsorbable. While an absorbable barrier (for example, a barrier made of oxidized regenerated cellulose) would be preferable, not all studies have demonstrated the efficacy of such barriers in preventing adhesions. Liquid barriers have also been considered for use in preventing adhesions; for example, chondroitin sulfate and carboxymethyl cellulose have both shown some promise in animal models. In addition, solutions of dextran 70 (molecular weight =70,000) have been the subject of a number of clinical studies. Not all clinical evaluations of 32% dextran 70 have found a therapeutic effect, however, and the clinical use of the solution is also associated with clinically important side effects.

Anti-inflammatory drugs have been evaluated for their effects on postoperative adhesion formation, as they may limit the release of fibrinous exudate in response to inflammation at the surgical site. Two general classes of these drugs were tested: corticosteroids and nonsteroidal anti-inflammatory drugs. The results of corticosteroid use in

animal studies have generally not been encouraging, and clinical use of corticosteroids is limited by their other pharmacologic properties. While experimental evaluations of nonsteroidal anti-inflammatory drugs in postoperative adhesion formation show promise, clinical evaluations of these drugs for adhesion prevention is needed.

The third approach explored to date involves the removal of fibrin deposits. Although proteolytic enzymes (e.g., pepsin, trypsin and papain) should theoretically augment the local fibrinolytic system and limit adhesion formation, these enzymes are rapidly neutralized by peritoneal exudates rendering them virtually useless for adhesion prophylaxis. While various fibrinolytics (for example, fibrinolysin, streptokinase and urokinase) have been advocated, a potential complication to the clinical use of these enzymes in postoperative therapy is excessive bleeding resulting from their administration. Topical application of a recombinant tissue plasminogen activator (rt-PA) has been shown to reduce adhesion formation in a variety of animal models; further research is necessary to develop suitable delivery systems to provide drug to the surgical site and identify the postoperative time when adhesion prevention is feasible.

To date, no single therapeutic approach has proven universally effective in preventing formation of postoperative intraperitoneal adhesions. Therefore, there is a need for compositions and methods which may be used safely and effectively to prevent adhesion formation in a variety of different contexts.

It is an object of the present invention to provide compositions and methods for the minimization or prevention of post-surgical adhesion formation.

### SUMMARY OF THE INVENTION

In accordance with one aspect of the present invention, there is provided a composition for the minimization or prevention of adhesion formation comprising at least one peptide containing the amino acid sequence Arg-Gly-Asp in a drug delivery system which maintains an effective concentration of the peptide at a site of potential adhesion formation. The peptide containing the requisite amino acid sequence is further characterized in that it inhibits platelet aggregation and does not induce inflammation or trauma at the site of administration. Pursuant to another aspect of the present invention, adhesion formation is minimized or prevented by administration of at least one peptide containing the amino acid sequence Arg-Gly-Asp at a site of potential adhesion formation for a period of time sufficient to permit substantial tissue repair (e.g., re-epithelialization or mesothelial repair) at the site.

### DETAILED DESCRIPTION OF THE INVENTION

The inventive composition and method are useful in minimizing or preventing adhesion formation, the most common cause of which is prior surgery. The inventive composition and method have been shown to be particularly effective in preventing adhesion formation in the peritoneum following surgery. In addition, the present invention finds utility in other contexts, e.g., for cardiovascular, orthopedic, thoracic, ophthalmic, CNS and other uses, where prevention of the formation of adhesions is a significant concern. For the purposes of the following discussion, attention is directed primarily to description of compositions and methods useful in inhibiting peritoneal adhesion formation.

The present invention contemplates the use of at least one non-naturally-occurring peptide containing the amino acid