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May 5, 1991

Dr. Steve Lewis
Office of Naval Research
Combat Casualty Care Research Area
Naval Medical Research & Development Command
Naval Medical Command, National Capitol Region
Code 405
Bethesda, MD 20814-5044

Subject: Quarterly Report for Award N00014-90-J1797
Liquid Collagen Wound Coverings

Dear Dr. Lewis:

Attached is a brief summary of research progress since our last report of December 10, 1990. As you will recall you had earlier recommended that I adopt a four monthly reporting schedule, rather than a quarterly reporting schedule.

Yours sincerely,

J. Peter Bentley, PhD
Professor of Biochemistry
and Molecular Biology

cc: Administrative Grants Officer
Director, Naval Research Laboratory
Defense Technical Information Center
Office of Chief of Naval Operations
Bureau of Medicine and Surgery

Liquid Collagen Wound Coverings Award Number N00014-90-J1797 Quarterly Report
May 5, 1991

Introduction

Captain Steven Lewis, MD, visited the laboratory in March, 1991, and met with all of the staff to discuss progress on this project. In addition, he met with Alan Seyfer, MD, Professor of Surgery, Chief of Plastic and Reconstructive Surgery, to discuss future projects of interest.

Collagen Preparation

Since the last report on December 10, two additional batches of collagen have been prepared and microbiological studies carried out with a contract laboratory (Consulting Clinical Microbiological Labs, Portland, Oregon). The last two batches have proved to be sterile after culture for seven days in several different kinds of medium. We have modified our storage procedure and the recent batches are now stored in 0.01 M HCL at liquid nitrogen temperatures, which simplifies the reconstitution when the batches are to be used.

Sterilization of Collagen Preparations

In an attempt to overcome the fragmentation produced when freeze dried collagen preparations are subjected to gamma irradiation, we have added DOPA at a concentration of 10^{-3} M prior to freeze drying. These preparations were subsequently exposed to varying amounts of gamma irradiation up to 2.5 megarads. Dramatic stabilization of the collagen was seen after the addition of DOPA. We propose this is because DOPA acts as a free radical sink and thus protects against free radical damage induced by the radiation. To extend this study we have recently exposed collagen preparations to gamma irradiation after the addition of other free radical sinks, hypotaurine and taurine (as a control). Initial polyacrylamide gel studies show similar protection to that earlier noted with DOPA. These studies are ongoing.

Covalent Binding of DOPA

The experiments attempting to covalently bind a crosslinking agent (L-DOPA) to collagen by activating either the collagen or the DOPA with EDAC are continuing with no major progress to report at this time.

Human Studies

We have currently enrolled six additional patients with split thickness skin graft donor sites in the clinical trials of our collagen pourable wound dressing. All patients have tolerated the application well and there have been no adverse reactions noted. In addition, there has been no incidence of infection.

We have expanded the study group to include more complicated wounds, i.e. venous stasis ulcers and partial thickness burns. These wounds are an obvious next step in the evaluation of any topical wound therapy and offer the additional advantage of providing more objective data for comparison. Addenda have been submitted to the human use committee at OHSU and at the Portland VA Medical Center to include these wounds. In addition, we have contacted Dr. Phillip Parshley, Chief of the burn unit at Emanuel Hospital. He will likely be collaborating with us, which should vastly increase our patient population in the near future.

Vehicle for Growth Factors

Our studies using collagen as a delivery vehicle for growth factors are underway. Initial results using collagen ring implants, crosslinked with DOPA, implanted subpectorally in rats, reveal that they are present and maintain their shape for at least 28 days. Previous experience has shown that we see osteogenesis after 28 days with osteogenin provided it is in a vehicle which "holds it in place." Others have had similar observations using PDGF and TGF-b, i.e., that the longer it is maintained in proximity, the more effective it is. The fact that dopacol is not degraded in this period and that it can theoretically be incorporated by the native tissues, encourages it use as a delivery vehicle.

We are now beginning a trial with osteogenin/dopacol implants and will soon be looking at topical application of PDGF/collagen as a pseudodermis.