# General Immune Health Research

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| Citation | Abstract |
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| Carolina Salvador, Bing Li, Richard Hansen, Daniel E. Cramer, Maiying Kong and Jun Yan<br><br>**Yeast-Derived β-Glucan Augments the Therapeutic Efficacy Mediated by Anti–Vascular Endothelial Growth Factor Monoclonal Antibody in Human Carcinoma Xenograft Models**<br><br>Clinical Cancer Research 2008;1239 14(4) February 15, 2008 | Bevacizumab is a recombinant IgG1 humanized monoclonal antibody against vascular endothelial growth factor (VEGF). Its proposed mechanism of action is independent of immune effector functions. Many human carcinomas not only secrete VEGF but also express membrane-bound VEGF. In addition, VEGF receptors are expressed on tumor cells. It is hypothesized that bevacizumab could bind membrane-bound VEGF or VEGF-VEGF receptor complexes on tumors, thereby initiating potential immunologic consequences. We previously showed that yeast-derived β-glucan functions with antitumor antibodies that activate complement to recruit complement receptor 3–expressing leukocytes capable of mediating complement receptor 3–dependent cellular cytotoxicity of tumors opsonized with iC3b. In the current study, the therapeutic efficacy mediated by combining bevacizumab with yeast-derived β-glucan was studied in human carcinoma xenograft models. Results: Human ovarian carcinoma SKOV-3 cells expressed membrane-bound VEGF both in vitro and in vivo. Bevacizumab was bound to membrane-bound VEGF, activated complement, and synergized with β-glucan to elicit cellular cytotoxicity in vitro. In vivo study showed that β-glucan could significantly augment the therapeutic efficacy mediated by bevacizumab. Conclusions: Yeast-derived β-glucan can synergize with anti-VEGF monoclonal antibody bevacizumab for the treatment of cancer with membrane-bound VEGF expression. |
| Bing Li, Daniel J. Allendorf, Richard Hansen, Jose Marroquin, Chuanlin Ding, Daniel E. Cramer and Jun Yan<br><br>**Yeast β-Glucan Amplifies Phagocyte Killing of iC3b-opsonized Tumor Cells via CR3-Syk-PI3-kinase Pathway**<br><br>The Journal of Immunology, 2006, Aug 1;177(3):1661-9.<br><br>PMID: 16849475 [PubMed - indexed for MEDLINE] | Anti-tumor mAbs hold promise for cancer therapy, but are relatively inefficient. Therefore, there is a need for agents that might amplify the effectiveness of these mAbs. One such agent is β-glucan, a polysaccharide produced by fungi, yeast, and grains, but not mammalian cells. β-glucans are bound by C receptor 3 (CR3) and, in concert with target-associated complement fragment iC3b, elicit phagocytosis and killing of yeast. β-glucans may also promote killing of iC3b-opsonized tumor cells engendered by administration of anti-tumor mAbs. In this study, we report that tumor-bearing mice treated with a combination of β-glucan and an anti-tumor mAb show almost complete cessation of tumor growth. This activity evidently derives from a 25-kDa fragment of β-glucan released by macrophage processing of the parent polysaccharide. This fragment, but not parent β-glucan, binds to neutrophil CR3, induces CBRM 1/5 neoepitope expression, and elicits CR3-dependent cytotoxicity. These events require phosphorylation of the tyrosine kinase, Syk, and consequent PI3K activation because β-glucan-mediated CR3-dependent cytotoxicity is greatly decreased by inhibition of these signaling molecules. Thus, β-glucan enhances tumor killing through a cascade of events, including in vivo macrophage cleavage of the polysaccharide, dual CR3 ligation, and CR3-Syk-PI3K signaling. These results are important inasmuch as β-glucan, an agent without evident toxicity, may be used to amplify tumor cell killing and may open new opportunities in the immunotherapy of cancer. |
| Daniel J. Allendorf, Jun Yan, Gordon D. Ross, Richard D. Hansen, Jarek T. Baran, Krishnaprasad Subbarao, Li Wang, and Bodduluri Haribabu<br><br>**C5a-Mediated Leukotriene B4-Amplified Neutrophil Chemotaxis Is Essential in Tumor Immunotherapy Facilitated by Anti-Tumor Monoclonal Antibody and β-Glucan**<br><br>The Journal of Immunology, 2005, 174: 7050–7056. | Intravenous and orally administered β-glucans promote tumor regression and survival by priming granulocyte and macrophage C receptor 3 (CR3, iC3bR and CD11b/CD18) to trigger the cytotoxicity of tumor cells opsonized with iC3b via anti-tumor Abs. Despite evidence for priming of macrophage CR3 by oral β-glucan in vivo, the current study in C57BL/6 and BALB/c mice showed that granulocytes were the essential killer cells in mAb- and oral β-glucan-mediated tumor regression, because responses were absent in granulocyte-depleted mice. Among granulocytes, neutrophils were the major effector cells, because tumor regression did not occur when C5a-dependent chemotaxis was blocked with a C5aR antagonist, whereas tumor regression was normal in $C3aR^{-}/^{-}$ mice. Neutrophil recruitment by C5a in vivo required amplification via leukotriene B4, because both C5a-mediated leukocyte recruitment into the peritoneal cavity and tumor regression were suppressed in leukotriene B4R-deficient ($BLT\text{-}1^{-}/^{-}$) mice. |

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| PMID: 15905548 [PubMed - indexed for MEDLINE] | |
| Jun Yan, Daniel J Allendorf & Brian Brandley<br><br>**Yeast Whole Glucan Particle ß-Glucan in Conjunction with Anti-tumour Monoclonal Antibodies to Treat Cancer**<br><br>Expert Opinion on Biological Therapy May 2005, Vol. 5, No. 5, Pages 691-702<br><br>PMID: 15934844 [PubMed - indexed for MEDLINE] | Beta-glucans, biological response modifiers (BRMs) derived from the cell walls of yeast and other sources, have been demonstrated to prime leukocyte complement receptor 3 (CR3), thus enabling these cells to kill tumours opsonised with complement fragment iC3b. Many tumours activate complement via the classical pathway mediated by antitumour monoclonal antibodies (mAbs) or natural antibodies. Studies into the cellular and molecular mechanisms of action have demonstrated that orally administrated yeast β-glucans are ingested and processed by macrophages. These macrophages secrete the active moiety that primes neutrophil CR3 to kill iC3b-opsonised tumour cells. Extensive studies in preclinical animal tumour models have demonstrated the efficacy of combined oral particulate yeast β-glucan with antitumour mAb therapy in terms of tumour regression and long-term survival. It is proposed that the addition of β-glucan will further improve the clinical therapeutic efficacy of antitumour mAbs in cancer patients. |
| Feng Hong, Jun Yan, Jarek T. Baran, Daniel J. Allendorf, Richard D. Hansen, Gary R. Ostroff, Pei Xiang Xing, Nai-Kong V. Cheung, and Gordon D. Ross<br><br>**Mechanism by Which Orally Administered β-1,3-Glucans Enhance the Tumoricidal Activity of Antitumor Monoclonal Antibodies in Murine Tumor Models**<br><br>The Journal of Immunology, 2004, 173: 797–806.<br><br>PMID: 15240666 [PubMed - indexed for MEDLINE] | Antitumor mAb bind to tumors and activate complement, coating tumors with iC3b. Intravenously administered yeast β-1,3; 1,6-glucan functions as an adjuvant for antitumor mAb by priming the inactivated C3b (iC3b) receptors (CR3; CD11b/CD18) of circulating granulocytes, enabling CR3 to trigger cytotoxicity of iC3b-coated tumors. Recent data indicated that barley β-1,3; 1,4-glucan given orally similarly potentiated the activity of antitumor mAb, leading to enhanced tumor regression and survival. This investigation showed that orally administered yeast β-1,3;1,6-glucan functioned similarly to barley β-1,3;1,4-glucan with antitumor mAb. With both oral β-1,3-glucans, a requirement for iC3b on tumors and CR3 on granulocytes was confirmed by demonstrating therapeutic failures in mice deficient in C3 or CR3. Barley and yeast β-1,3-glucan were labeled with fluorescein to track their oral uptake and processing in vivo. Orally administered β-1,3-glucans were taken up by macrophages that transported them to spleen, lymph nodes, and bone marrow. Within the bone marrow, the macrophages degraded the large β-1,3-glucans into smaller soluble β-1,3-glucan fragments that were taken up by the CR3 of marginated granulocytes. These granulocytes with CR3-bound β-1,3-glucan-fluorescein were shown to kill iC3b-opsonized tumor cells following their recruitment to a site of complement activation resembling a tumor coated with mAb. |
| Hong, F., Hansen, R. D., Yan, J., Allendorf, D. J., Baran, J. T., Ostroff, G. R., and Ross, G. D.<br><br>**β-Glucan Functions as an Adjuvant for Monoclonal Antibody Immunotherapy by Recruiting Tumoricidal Granulocytes as Killer Cells**<br><br>Cancer Research, 63(24):9023-31, Dec. 15, 2002.<br><br>PMID: 14695221 [PubMed – indexed for Medline] | The tumor-killing mechanisms available to monoclonal antibodies (mAbs; *e.g.* antagonism of growth factor receptors, antibody-dependent cell-mediated cytotoxicity) limit efficacy. Previous studies suggested that i.v. β-glucan might function as an adjuvant for antitumor mAbs. β-glucan had been shown to function via the iC3b-receptor complement receptor 3 (CR3; CD11b/CD18) thereby enhancing leukocyte killing of tumor cells coated with iC3b via naturally occurring antitumor antibodies. Therapy with β-Glucans was limited by levels of natural antibodies and by tumor escape through elimination of antigen-positive cells. Accordingly, it was hypothesized that β-glucan responses could be improved by combined administration with antitumor mAbs. Five tumor models were explored in BALB/c or C57B1/6 mice using tumors that expressed either high levels of naturally occurring antigens (*e.g.* $G_{D2}$ ganglioside) or recombinant human MUC1. In comparison with antitumor mAb or β-glucan alone, combined treatment with mAb plus β-Glucan produced significantly greater tumor regression in all models that included mammary, s.c., and hepatic tumors. Tumor-free survival only occurred in models that incorporated stable expression of the target antigen. β-Glucan enhancement of the mAb tumoricidal response did not occur in mice deficient in either leukocyte CR3 ($CD11b^{-/-}$) or serum C3, confirming the requirement for CR3 on leukocytes and iC3b on tumors. Granulocytes appeared to be primarily responsible for tumoricidal activity, |

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| | because β-Glucan therapeutic responses did not occur in granulocyte-depleted mice. These data suggest that they therapeutic efficacy of mAbs known to activate complement (e.g. Herceptin, Rituxan and Erbitux) could be significantly enhanced if they were combined with β-Glucan. |
| Ross GD, Vetvicka V, Yan J, Xia Y, Vetvickova J.<br><br>**Therapeutic intervention with complement and beta-glucan in cancer.**<br><br>*Immunopharmacology*. 1999 May; 42(1-3):61-74. Review.<br><br>PMID: 10408367 [PubMed - indexed for MEDLINE] | Complement (C) has two major effector systems available for host defense. The membrane attack complex (MAC) generated from components C5-C9 can form membrane-penetrating lesions that lead to cell death by causing a rapid loss of cytoplasmic components. The MAC is only effective against pathogens with outer phospholipid membranes, and cannot kill gram-positive bacteria or yeast whose membranes are protected by cell walls. The most important effector mechanism of C is the opsonization of microbial pathogens with the serum protein C3 that leads to their high avidity attachment to the C3-receptors of phagocytic cells. Pathogens that activate complement are first coated with the C3b fragment of C3, which is rapidly proteolyzed into the iC3b fragment by serum factor I. These iC3b fragments serve to promote the high avidity attachment of the 'iC3b-opsonized' pathogens to the iC3b-receptors (CR3, CD11b/CD18) of phagocytic cells and natural killer (NK) cells, stimulating phagocytosis and/or cytotoxic degranulation. Host cells, including neoplastic tumor cells, have been endowed with natural mechanisms for self-protection against both the MAC and the cytotoxic activation of CR3. This review discusses a novel type of immunotherapy for cancer that uses soluble yeast beta-glucan to override the normal resistance of iC3b-opsonized tumor cells to the cytotoxic activation of phagocyte and NK cell CR3, allowing this important effector mechanism of the C system to function against tumor cells in the same way that it normally functions against bacteria and yeast. Moreover, the cytotoxic activation of beta-glucan-primed NK cell CR3 by iC3b-opsonized tumors is shown to be accompanied by a tumor-localized secretion of the cytokines TNFalpha, IFNalpha, IFNgamma, and IL-6. |
| Yan, J., Větvička, V., Xia, Y., Coxon, A., Carroll, M.C., Mayadas, T.N., and Ross, G.D.<br><br>**β-Glucan, a "specific" biologic response modifier that uses antibodies to target tumors for recognition by complement receptor 3 (CD11b/CD18).**<br><br>*J. Immunol.,* 163:3045-3052, 1999.<br><br>PMID: 10477568 [PubMed - indexed for MEDLINE] | Beta-Glucans were identified 36 years ago as a biologic response modifier that stimulated tumor rejection. In vitro studies have shown that beta-glucans bind to a lectin domain within complement receptor type 3 (CR3; known also as Mac-1, CD11b/CD18, or alphaMbeta2-integrin, that functions as an adhesion molecule and a receptor for factor I-cleaved C3b, i.e., iC3b) resulting in the priming of this iC3b receptor for cytotoxicity of iC3b-opsonized target cells. This investigation explored mechanisms of tumor therapy with soluble beta-glucan in mice. Normal mouse sera were shown to contain low levels of Abs reactive with syngeneic or allogeneic tumor lines that activated complement, depositing C3 onto tumors. Implanted tumors became coated with IgM, IgG, and C3, and the absent C3 deposition on tumors in SCID mice was reconstituted with IgM or IgG isolated from normal sera. Therapy of mice with glucan- or mannan-rich soluble polysaccharides exhibiting high affinity for CR3 caused a 57-90% reduction in tumor weight. In young mice with lower levels of tumor-reactive Abs, the effectiveness of beta-glucan was enhanced by administration of a tumor-specific mAb, and in SCID mice, an absent response to beta-glucan was reconstituted with normal IgM or IgG. The requirement for C3 on tumors and CR3 on leukocytes was highlighted by therapy failures in C3- or CR3-deficient mice. Thus, the tumoricidal function of CR3-binding polysaccharides such as beta-glucan in vivo is defined by natural and elicited Abs that direct iC3b deposition onto neoplastic cells, making them targets for circulating leukocytes bearing polysaccharide-primed CR3. Therapy fails when tumors lack iC3b, but can be restored by tumor-specific Abs that deposit iC3b onto the tumors. |

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| Xia, Y., Větvička, V., Yan, J., Hanikýřová, M., Mayadas, T. N., and Ross, G. D.<br><br>**The β-glucan-binding lectin site of mouse CR3 (CD11b/CD18) and its function in generating a primed state of the receptor that mediates cytotoxic activation in response to iC3b-opsonized target cells.**<br><br>*J. Immunol.,* 162:2281-2290, 1999<br><br>PMID: 9973505 [PubMed - indexed for MEDLINE] | Mouse leukocyte CR3 (Mac-1, alphaMbeta2 integrin) was shown to function as a receptor for beta-glucans in the same way as human CR3. Soluble zymosan polysaccharide (SZP) or pure beta-glucans labeled with FITC or 125I bound in a saturable and reversible manner to neutrophils, macrophages, and NK cells. This lectin activity was blocked by anti-CD11b mAb M1/70 or 5C6 and did not occur with leukocytes from CR3-/- (CD11b-deficient) mice. SZP preparations containing primarily mannose or glucose bound to CR3, and the binding of 125I-labeled beta-glucan to CR3 was competitively inhibited by beta-glucans from barley or seaweed, but not by yeast alpha-mannan. Also, as with human CR3, the lectin site of mouse CR3 was inhibited by alpha- or beta-methylglucoside (but not D-glucose), alpha- or beta-methylmannoside, and N-acetyl-D-glucosamine. Phagocytosis of zymosan and serum-opsonized zymosan was partially inhibited by anti-CR3 and was reduced to <40% of normal with leukocytes from CR3-/- mice. As with neutrophils from patients with CD18 deficiency, neutrophils from CR3-/- mice exhibited no phagocytosis of particulate beta-glucan. SZP or beta-glucans primed CR3 of neutrophils, macrophages, and NK cells for cytotoxicity of iC3b-opsonized tumor cells that otherwise did not trigger killing. beta-Glucan priming for cytotoxicity was inhibited by anti-CR3 and did not occur with leukocytes from CR3-/- mice. The primed state of macrophage and NK cell CR3 remained detectable for 18 to 24 h after pulsing with beta-glucans. The similarity of mouse and human CR3 in response to beta-glucans highlights the utility of mouse tumor models for development of therapeutic beta-glucans. |
| Větvička, V., Thornton, B. P., Wieman, T. J., and Ross, G. D.<br><br>**Targeting of NK cells to mammary carcinoma via naturally occurring tumor cell-bound iC3b and β-glucan-primed CR3 (CD11b/CD18).**<br><br>*J. Immunol.,* 159:599-605, 1997.<br><br>PMID: 9218574 [PubMed - indexed for MEDLINE] | Previous reports have suggested that malignant cells frequently generate a humoral immune response that is ineffective in tumor destruction. Despite coating tumors with IgM and IgG that activate the C system via the classical pathway, normal membrane regulators of C (e.g., membrane cofactor protein and CD59) prevent cytotoxicity. Moreover, C3 deposition on tumors does not result in cytotoxic recognition by phagocytes or NK cells bearing C3 receptors capable of mediating destruction of C3-opsonized bacteria or yeast. The current investigation showed that freshly excised mammary tumors bore IgM, IgG, and C3 detectable by flow cytometry. Normal sera contained natural IgM and IgG Abs reactive with breast tumor cell lines, and IgG Ab titers were increased in patients with breast cancer. Breast tumor cell lines incubated in normal serum from AB+ individuals activated the classical, but not the alternative, pathway of C and became coated with C3. Despite exhibiting membrane-bound C3, serum-opsonized breast tumor cell lines were not killed by CR3 (CD11b/CD18)-bearing NK cells. Priming of NK cell CR3 with small soluble yeast beta-glucan polysaccharides enabled CR3-dependent killing of these same C3-bearing tumor cell lines. Tests of mammary carcinoma cells from freshly excised tumors demonstrated that they also bore sufficient amounts of opsonic C3 for cytotoxic recognition by NK cells bearing polysaccharide-primed CR3, whereas they were largely resistant to NK cells bearing unprimed CR3. This study demonstrates the potential utility of using naturally occurring opsonic C3 on tumor cells for specific immunotherapeutic targeting by NK cells and phagocytes bearing polysaccharide-primed CR3. |
| Větvička, V., Thornton, B. P., and Ross, G. D.<br><br>**Soluble β-glucan polysaccharide binding to the lectin site of neutrophil or NK cell complement receptor type 3 (CD11b/CD18) generates a primed state of the receptor capable of mediating cytotoxicity of iC3b-opsonized target cells.** | When phagocyte CR3 binds to iC3b on bacteria or yeast, phagocytosis and degranulation are triggered because of simultaneous recognition of iC3b via a CD11b I-domain binding site and specific microbial polysaccharides via a lectin site located COOH-terminal to the I-domain. By contrast, when phagocyte or natural killer (NK) cell CR3 adheres to iC3b on erythrocytes or tumor cells that lack CR3-binding membrane polysaccharides, neither lysis nor cytotoxicity are stimulated. This investigation showed that soluble CR3-specific polysaccharides such as beta-glucan induced a primed state of CR3 that could trigger killing of iC3b-target cells that were otherwise resistant to cytotoxicity. Anti-CR3 added before sugars prevented priming, whereas anti-CR3 added after sugars blocked primed CR3 attachment to iC3b-targets. Polysaccharide priming required |

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| *J. Clin. Invest.,* 98:50-61, 1996.<br><br>PMID: 8690804 [PubMed - indexed for MEDLINE] | tyrosine kinase(s) and a magnesium-dependent conformational change of the I-domain that exposed the CBRM1/5 activation epitope. Unlike LPS or cytokines, polysaccharides did not up-regulate neutrophil CR3 expression nor expose the mAb 24 reporter epitope representing the high affinity ICAM-1-binding state. The current data apparently explain the mechanism of tumoricidal beta-glucans used for immunotherapy. These polysaccharides function through binding to phagocyte or NK cell CR3, priming the receptor for cytotoxicity of neoplastic tissues that are frequently targeted with iC3b and sparing normal tissues that lack iC3b. |
| Sveinbjornsson B, Olsen R, Seternes OM, Seljelid R.<br><br>**Macrophage cytotoxicity against murine meth A sarcoma involves nitric oxide-mediated apoptosis.**<br><br>*Biochem Biophys Res Commun.* 1996 Jun 25;223(3):643-9.<br><br>PMID: 8687449 [PubMed] | We have studied the cytotoxic effect of stimulated macrophages on Meth A tumor cells in vitro. When stimulated with interferon-gamma and soluble beta-1,3-D-glucan, macrophages exerted cytotoxicity towards syngeneic Meth A tumor cells. This cytotoxicity was associated with a high level of nitric oxide production. Both cell death and nitric oxide production were significantly inhibited by the addition of aminoguanidine, a specific inhibitor of inducible nitric oxide synthase (iNOS), to the culture medium. The cytotoxic effect was accompanied by internucleosomal cleavage of DNA as shown by electrophoresis and DNA fragmentation assay. |
| Kournikakis B, Mandeville R, Brousseau P, Ostroff G<br><br>**Anthrax-Protective Effects of Yeast Beta 1,3 Glucans**<br><br>*MedGenMed.* 2003 March 24. | **Context**<br>The recent events increasing the threat of bioterrorism have prompted a widespread search for defenses against this peril.<br><br>**Objective**<br>To evaluate the anthrax-protective effect of β1,3-glucan immune modulators (PGG-Glucan and WGP Beta Glucan) in an experimental animal model.<br><br>**Design**<br>β1,3-glucan immune modulators were administered by subcutaneous injection to Balb/c mice 2 days prior to anthrax challenge. WGP Beta Glucan was administered by daily oral gavage for 7 days prior to challenge, or in drinking water for 10 days post-challenge with a lethal dose of *B. anthracis* spores. Survival, survival time and microbial bioburden relative to an infected, untreated control group were assessed.<br><br>**Results**<br>A single injected dose of PGG-Glucan or WGP Beta Glucan immune modulators given two days before challenge significantly: a) increased the survival rate of infected mice (2.5-fold), b) diminished the bacterial load in the lungs of infected mice (4-8 fold), and c) increased the proportion of bacteria-free animals 10 days after challenge (2-fold). In mice prophylactically administered oral WGP Beta Glucan for one week prior to infection, survival increased from 50 to 100%; therapeutic administration of oral WGP Beta Glucan for ten days post-infection increased survival from 30% up to 90% in treatment groups.<br><br>**Conclusions**<br>These results demonstrate the potential for β1,3-glucan immune modulators to provide a significant degree of protection against anthrax, a potential biological warfare (BW) agent in a mouse model of anthrax infection. Further studies are needed to optimize protection, evaluate activity in combination with other treatment options, demonstrate activity in a validated primate model of infection, and determine if protection is effective against other potential BW agents. |

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| Vetvicka, V, Terayama K, Mandeville R, Brousseau P, Kournikakis B, Ostroff G<br><br>**Orally-administered Yeast β1,3-glucan prophylactically protects against anthrax infection and cancer in mice**<br><br>*Journal of the American Nutraceutical Association*. Vol. 5, No. 2, Spring 2002: 16-20. | β1,3-glucans from various bacterial, mushroom, yeast, and cereal sources have been established as immunomodulators. In the present paper we demonstrate that orally-administered yeast β1,3-glucan had significant effects as a prophylactic treatment to reduce the mortality of anthrax infection in mice. In addition, the same type of treatment also inhibited the growth of metastatic cancer cells *in vivo.* The mechanism of action involves the stimulation of three important cytokines: IL-2, IFN-γ, and TNF-α. These results provide preclinical evidence for the beneficial effects of orally-administered yeast β1,3-glucan. |
| Liang, J., D. Melican, L. Cafro, G. Palace, L. Fisette, R. Armstrong, and M. L. Patchen.<br><br>**Enhanced clearance of a multiple antibiotic-resistant *Staphylococcus aureus* in rats treated with PGG-glucan is associated with increased leukocyte counts and increased neutrophil oxidative burst activity**.<br><br>*Int. J. Immunopharmacol*. 1998. 20:595-614**.**<br><br>PMID: 9848393 [PubMed - indexed for MEDLINE] | PGG-Glucan [Betafectin], a highly purified soluble beta-(1-6)-branched beta-(1 3)-linked glucan isolated from *Saccharomyces cerevisiae*, has broad in vitro and in vivo anti-infective activities unrelated to cytokine induction. Here we present in vivo results on the anti-infective activity of PGG-Glucan against a multiple antibiotic resistant *Staphylococcus aureus*. PGG-Glucan (0.25-4 mg/kg) was administered intramuscularly to male Wistar rats 48 h, 24 h, and 4 h before and 4 h after intraperitoneal implantation of a gelatin capsule containing 10(8)S. aureus colony forming units (CFU). Blood samples were collected at various times after challenge to determine CFU levels, leukocyte counts and neutrophil oxidative burst activity; serum TNF-alpha, and IL-1beta levels were also evaluated. The 0.25 mg/kg PGG-Glucan dose had no effect on reducing blood CFU levels; however, PGG-Glucan doses of 0.5 mg/kg, 1 mg/kg, 2 mg/kg or 4 mg/kg significantly reduced blood CFU levels by 48 h after challenge. Reduced CFU levels correlated with significantly elevated absolute monocyte counts, absolute neutrophil counts, and neutrophil oxidative burst activity in the absence of any effect on TNF-alpha or on IL-1beta levels. In additional studies, effects on mortality and blood CFU levels were evaluated in rats treated with ampicillin (an antibiotic to which the *S. aureus* was resistant), PGG-Glucan, or both agents. Mortality and blood CFU levels were reduced most in combination-treated rats compared to saline control rats or rats treated with either ampicillin alone or PGG-Glucan alone. We conclude that in vivo (1) PGG-Glucan can enhance clearance of an antibiotic resistant *S. aureus*, (2) that this clearance is accompanied by an increase in monocytes and neutrophils as well as a potentiation of neutrophil oxidative microbiocidal activity without alteration of the proinflammatory cytokine response, and (3) PGG-Glucan can enhance the effectiveness of traditional antibiotic treatment. |

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| Dellinger EP, Babineau TJ, Bleicher P, Kaiser AB, Seibert GB, Postier RG, Vogel SB, Norman J, Kaufman D, Galandiuk S, Condon RE.<br><br>**Effect of PGG-glucan on the rate of serious postoperative infection or death observed after high-risk gastrointestinal operations. Betafectin Gastrointestinal Study Group.**<br><br>Arch Surg. 1999 Sep;134(9):977-83.<br><br>PMID: 10487593 [PubMed - indexed for MEDLINE] | **Background**: Postoperative infections remain common after high-risk gastrointestinal procedures. PGG-glucan (Betafectin; Alpha Beta Technology Inc, Worcester, Mass), derived from yeast cell walls, promotes phagocytosis and intracellular killing of bacterial pathogens by leukocytes, prevents infection in an animal model of wound infection, and acts synergistically with antibiotics to reduce mortality in rat peritonitis.<br><br>**Hypothesis**: We hypothesized that infectious complications in these patients might be reduced by the administration of a nonspecific immune-enhancing agent.<br><br>**Design**: Multicenter, prospective, randomized, double-blind, placebo-controlled trial of 1249 patients prospectively stratified into colorectal or noncolorectal strata.<br><br>**Setting**: Thirty-nine medical centers throughout the United States.<br><br>**Patients**: Aged 18 years or older, scheduled for gastrointestinal procedure lasting 2 to 8 hours, with 2 or more defined risk factors.<br><br>**Interventions**: PGG-glucan, 0.5 mg/kg or 1.0 mg/kg, or placebo once preoperatively and 3 times postoperatively. All patients received standardized antibiotic prophylaxis.<br><br>**Main Outcome Measures**: Serious infection or death within 30 days. |
| | **Results**: All randomized patients revealed no difference in serious infections and deaths in the treated groups compared with placebo groups (15% vs 14%, P>.90). In the prospectively defined noncolorectal stratum (n = 391), PGG-glucan administration was associated with a statistically significant relative reduction (39%) in serious infections and death (placebo, 46 [36%] of 129 vs either PGG-glucan group, 29 [21%] of 132 and 28 [22%] of 130, P<.02). PGG-glucan reduced postoperative infection or death in malnourished patients having noncolorectal procedures (31 [44%] of 70, placebo group; 16 [24%] of 68, 0.5-mg/kg PGG-glucan group; 12 [17%] of 72, 1.0-mg/kg PGG-glucan group; P<.001). Study drug was stopped owing to adverse effects more frequently for patients receiving PGG-glucan than placebo (2%, 4%, and 7% for the placebo group, 0.5-mg/kg PGG-glucan group, and 1.0-mg/kg PGG-glucan group, respectively, P<.003).<br><br>**Conclusion**: Perioperative administration of PGG-glucan reduced serious postoperative infections or death by 39% after high-risk noncolorectal operations. |

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| Kaiser AB, Kernodle DS.<br><br>**Synergism between poly-(1-6)-beta-D-glucopyranosyl-(1-3)-beta-D-glucopyranose glucan and cefazolin in prophylaxis of staphylococcal wound infection in a guinea pig model.**<br><br>*Antimicrob Agents Chemother*. 1998 Sep;42(9):2449-51.<br><br>PMID: 9736583 [PubMed - indexed for MEDLINE] | To determine whether the infection-preventing capability of the neutrophil-activating agent poly-(1-6)-beta-D-glucopyranosyl-(1-3)-beta-D-glucopyranose glucan (PGG-glucan) can be enhanced with antibiotic prophylaxis, we administered PGG-glucan and cefazolin, alone and in combination, to guinea pigs inoculated with isolates of staphylococci. Guinea pigs receiving both PGG-glucan and cefazolin had 50% infective doses that were 8- to 20-fold higher than those obtained with cefazolin alone and 100- to 200-fold higher than those obtained with PGG-glucan alone. PGG-glucan and cefazolin are synergistic in their ability to prevent staphylococcal wound infection. |
| Tzianabos AO, Gibson FC 3rd, Cisneros RL, Kasper DL.<br><br>**Protection against experimental intraabdominal sepsis by two polysaccharide immunomodulators.**<br><br>*J Infect Dis.* 1998 Jul;178(1):200-6.<br><br>PMID: 9652441 [PubMed - indexed for MEDLINE] | Two immunomodulating polysaccharides, poly-(1-6)-beta-glucotriosyl-(1-3)-beta-glucopyranose (PGG)-glucan and Bacteroides fragilis polysaccharide A (PS A), were evaluated for the prevention of mortality and abscess formation associated with experimental intraabdominal sepsis. Prophylactic treatment with a combination of these compounds significantly reduced mortality (8% vs. 44% in the saline-treated control group) and the incidence of abscesses (30% vs. 100% in the saline-treated control group) after challenge with rat cecal contents. These compounds were also effective when administered therapeutically after bacterial contamination of the peritoneal cavity. PS A treatment conferred long-term protection against abscess formation and resulted in significantly fewer total aerobes and anaerobes in the peritoneal fluid of animals challenged with cecal contents. These data demonstrate the usefulness of two immunomodulatory polysaccharides in preventing experimental intraabdominal sepsis in the absence of antimicrobial therapy and may represent a new adjunct to antibiotic regimens currently used to prevent clinical cases of this disease. |
| Kernodle DS, Gates H, Kaiser AB.<br><br>**Prophylactic anti-infective activity of poly-[1-6]-beta-D-glucopyranosyl-[1-3]-beta-D-glucopryanose glucan in a guinea pig model of staphylococcal wound infection.**<br><br>*Antimicrob Agents Chemother*. 1998 Mar;42(3):545-9.<br><br>PMID: 9517930 [PubMed - indexed for MEDLINE] | The judicious use of perioperative antibiotic prophylaxis reduces the infectious complications of surgery. However, increased bacterial resistance within hospitals may make antibiotic prophylaxis less effective in the future and alternative strategies are needed. New immunomodulatory agents might prevent wound infections by stimulation of the host immune system. To test this hypothesis, we administered poly-[1-6]-beta-D-glucopyranosyl- [1-3] -beta-D-glucopyranose glucan (PGG glucan), which enhances neutrophil microbicidal activity, intravenously to guinea pigs in doses ranging from 0.015 to 4 mg/kg of body weight on the day before, on the day of, and on the day after intermuscular inoculation with methicillin-resistant strains of *Staphylococcus aureus* and *Staphylococcus epidermidis*. Abscesses were identified at 72 h, and median infective doses (ID50) and statistical significance were determined by logistic regression. Guinea pigs receiving PGG glucan and inoculated with methicillin-resistant *S. aureus* and *S. epidermidis* exhibited ID50 of as much as 2.5- and 60-fold higher, respectively, than those of control guinea pigs not receiving PGG glucan. Maximal protection was observed with a dose of 1 mg of PGG glucan per kg, and efficacy was reduced at higher as well as at lower PGG glucan doses. Furthermore, a single dose of PGG glucan given 24 h following bacterial inoculation was found to be effective in preventing infection. We conclude that PGG glucan reduces the risk of staphylococcal abscess formation. Neutrophil-activating agents are a novel means of prophylaxis against surgical infection and may be less likely than antibiotics to be affected adversely by the increasing antibiotic resistance of nosocomial pathogens. |

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| Hetland G, Lovik M, Wiker HG.<br><br>**Protective effect of beta-glucan against *mycobacterium bovis*, *BCG* infection in BALB/c mice.**<br><br>*Scand J Immunol.* 1998 Jun;47(6):548-53.<br><br>PMID: 9652822 [PubMed - indexed for MEDLINE] | Beta-1,3-glucan is a potent stimulator of macrophage functions and has a protective effect against a range of infections in rodent models. We examined whether the agent could also protect against the intracellular *Mycobacterium bovis*, bacillus *Calmette-Guerin* (BCG) infection in mice. *BCG*-susceptible BALB/cmice were injected intravenously (i.v.) with beta-glucan or vehicle 3 days before, or with beta-glucan 7 days after i.v. challenge with live *BCG* bacilli The animals were killed 4 or 8 weeks later, their organs were homogenized and applied to object slides and stained with auramin for counting of bacilli, or seeded onto agar in Petri dishes. Mice treated with beta-glucan both pre- and postchallenge had significantly lower numbers of *BCG* bacilli and *BCG* colony-forming units in spleen homogenates compared with controls 4 weeks after challenge. A similar, but not statistically significant, tendency was observed in spleen homogenates from mice killed 8 weeks after challenge. In homogenates of liver and lungs there were similar findings, but less pronounced. There was a dose-dependent effect of beta-glucan injected before BCG challenge on the number of *BCG* bacilli found in spleen and liver homogenates. In addition, antibody cross-reactivity was demonstrated between *M. tuberculosis* cell wall and beta-glucan. The results suggest that beta-glucan has a protective effect against *M. bovis*, *BCG* infection in susceptible mice. |
| Meira DA, Pereira PC, Marcondes-Machado J, Mendes RP, Barraviera B, Pellegrino Junior J, Rezkallah-Iwasso MT, Peracoli MT, Castilho LM, Thomazini I, Da Silva CL, Foss NT, Curi PR.<br><br>**The use of glucan as immunostimulant in the treatment of paracoccidioidomycosis.**<br><br>*Am J Trop Med Hyg*. 1996 Nov;55(5): 496-503.<br><br>PMID: 8940980 [PubMed - indexed for MEDLINE] | A group of 10 patients, nine of them seriously infected with *Paracoccidioides brasiliensis* (G1), received glucan (beta-1,3 polyglucose) as an immunostimulant intravenously once a week for one month, followed by monthly doses (10 mg) over an 11-month period, together with a specific anti-fungal agent as animmunostimulant. A second group of eight moderately infected patients (G2) was treated with only the anti-fungal agent. Among the patients in G1, there was only one case of relapse compared with five in G2. Values for the erythrocyte sedimentation rate (ESR) showed a significant difference ($P < 0.001$) post-treatment in G1 patients, when compared with the pretreatment levels. There was also a significant reduction ($P < 0.001$) in the level of serum antibodies to *P. brasiliensis* in the G1 patients in post-treatment examinations. The phytohemagglutinin (PHA) skin test showed a positive reaction among the patients in G1 ($P < 0.01$) post-treatment and there was a tendency towards an increase in the number of CD4+ T lymphocytes in both groups after treatment. The serum level of tumor necrosis factor (TNF) proved to be significantly higher ($P < 0.02$) in the G1 patients during treatment. In the G1 patients, the correlation between ESR and TNF tended to be negative whereas that between ESR and serum antibodies was positive. The present results indicate that the patients who received glucan, in spite of being more seriously ill, had a stronger and more favorable response to therapy. |

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| Compton R, Williams D, Browder W.<br><br>**The beneficial effect of enhanced macrophage function on the healing of bowel anastomoses.**<br><br>*Am Surg*. 1996 Jan;62(1):14-8.<br><br>PMID: 8540639 [PubMed - indexed for MEDLINE] | Inadequate healing and subsequent leakage of bowel anastomoses are serious postoperative complications in abdominal surgery. Previous studies have demonstrated the macrophage to be a key cell in the physiology of wound healing. The current study was undertaken to evaluate the effects of enhanced macrophage function on the healing of bowel anastomoses. Sprague-Dawley rats (250 gm) underwent laparotomy and jejunojejunostomy following IV treatment with glucan (100 mg per kg), a potent macrophage stimulant, or 5 per cent dextrose 24 hours before surgery and again on the day of surgery. Animals were killed and the anastomoses underwent wound tensiometry on Day 3 using a computer-assisted constant velocity tensiometer. The glucan-treated animals had a significantly greater anastomotic breaking strength (88.5 gm +/- 10.7 versus 45.45 gm +/- 5.1) ($P < 0.01$). Formalin fixation increased the breaking strength of the untreated anastomosis but not of the treated anastomosis (92.9 gm +/- 11.77 versus 92.3 +/- 12.44). Analysis of macrophage supernatant for the growth factors epidermal growth factor (EGF), platelet derived growth factor (PDGF), and transforming growth factor-beta (TGF-beta) was accomplished by immunoblot assay. Results indicated no difference in the presence of EGF in the stimulated and unstimulated macrophage supernatants. PDGF and TGF-beta were decreased in the stimulated macrophage supernatants. We conclude that 1) Enhanced macrophage function had a beneficial effect on the early tensile strength of bowel anastomoses. 2) Effects of the activated macrophage on bowel anastomoses may not be related to secretion of conventional growth factors. 3) Immunopharmacologic agents that enhance macrophage function may be an important adjunct to surgical therapy requiring bowel anastomosis. |
| Babineau TJ, Hackford A, Kenler A, Bistrian B, Forse RA, Fairchild PG, Heard S, Keroack M, Caushaj P, Benotti P.<br><br>**A phase II multicenter, double-blind, randomized, placebo-controlled study of three dosages of an immunomodulator (PGG-glucan) in high-risk surgical patients.**<br><br>*Arch Surg*. 1994 Nov;129(11):1204-10.<br><br>PMID: 7979954 [PubMed - indexed for MEDLINE] | **Objective**: To examine the safety and efficacy of multiple doses of PGG-glucan (poly-[1-6]-B-D-glucopyranosyl-[1-3]-B-D-glucopyranose) in high-risk patients undergoing major thoracic or abdominal surgery.<br><br>**Design**: An interventional, multicenter, double-blind, randomized, placebo-controlled study.<br><br>**Setting**: Four university-affiliated medical centers.<br><br>**Patients**: Sixty-seven high-risk patients undergoing major thoracic or abdominal surgery.<br><br>**Intervention**: Patients were randomized in a 1:1:1:1 ratio to receive saline placebo or PGG-glucan at a dose of 0.1 mg/kg, 0.5 mg/kg, and 1.0 mg/kg or 2.0 mg/kg. One dose was administered before surgery and three doses were administered after surgery.<br><br>**Main Outcome Measures**: To examine the safety and efficacy of PGG-glucan infusion and to identify potentially important factors for a planned phase III study.<br><br>**Results**: A dose-response trend with regard to infection incidence among patients who received PGG-glucan was observed. Serious infections occurred in four patients who received placebo and in three patients who received PGG-glucan at a dose of 0.1 mg/kg. However, only one patient who received PGG-glucan at a high dose had a serious infection. The incidence and severity of adverse events was comparable in all groups.<br><br>**Conclusions**: PGG-glucan was generally safe and well tolerated, may decrease postoperative infection rates, and warrants further investigation in a planned phase III trial. |

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| Pedroso M.<br><br>**Application of beta-1,3-glucan to prevent shipping fever in imported heifers.**<br><br>*Arch Med Res.* 1994 Summer;25(2):181.<br><br>PMID: 7919809 [PubMed - indexed for MEDLINE] | Particulated beta-1,3-glucan from *Saccharomyces cerevisiae* was evaluated to prevent shipping fever in imported heifers during the 15 days following their arrival to Cuba. Seventy seven animals received a single subcutaneous dose (5 mg/kg body weight) during the first 12 h following their arrival, whereas 44 served as untreated controls. Clinical symptoms were observed in 3 treated and 19 untreated animals ($p < 0.001$). One untreated heifer died. These observations confirm the usefulness of beta-1,3-glucan to prevent shipping fever. |
| de Felippe Junior J, da Rocha e Silva Junior M, Maciel FM, Soares Ade M, Mendes NF.<br><br>**Infection prevention in patients with severe multiple trauma with the immunomodulator beta 1-3 polyglucose (glucan).**<br><br>*Surg Gynecol Obstet.* 1993 Oct;177(4):383-8.<br><br>PMID: 8211583 [PubMed - indexed for MEDLINE] | In a effect to prevent nosocomial pneumonia and sepsis, we treated patients with severe multiple trauma with an immunomodulator--beta 1-3 polyglucose (glucan). Forty-one patients with no infection at admission were stratified using Trauma Score and included in a randomized double-blind controlled trial. They were divided into a control group (n = 20) and a glucan group (n = 21). Pneumonia occurred in 11 of 20 patients in the control group and in two of 21 recipients of glucan ($p < 0.01$). Sepsis occurred in seven of 20 patients in the control group and in two of 21 patients treated with glucan ($p < 0.05$). Considering patients with pneumonia and sepsis, a decrease was observed in nosocomial infection from 65.0 to 14.4 percent ($p < 0.001$). The mortality rate related to infection was 30.0 percent in patients in the control group and 4.8 percent in the group treated with glucan ($p < 0.05$). The general mortality rate, cerebral deaths excluded, was 42.1 percent in the control group and 23.5 percent in the glucan group. |
| Browder W, Williams D, Pretus H, Olivero G, Enrichens F, Mao P, Franchello A.<br><br>**Beneficial effect of enhanced macrophage function in the trauma patient.**<br><br>*Ann Surg.* 1990 May;211(5):605-12; discussion 612-3.<br><br>PMID: 2111126 [PubMed - indexed for MEDLINE] | Host immunosuppression after trauma contributes to septic morbidity. The macrophage is a key element in the host immune response. This study evaluated glucan, a macrophage stimulant, in a prospective, randomized, double-blind study of 38 trauma patients undergoing surgery. Glucan (21 patients), 50 mg/m2, or placebo (17 patients) was given intravenously daily for 7 days. Delayed hypersensitivity skin testing was performed on days 1 and 7 after trauma. Serum interleukin-1 (IL-1) and tumor necrosis factor (TNF) were assayed after trauma. While the total mortality rate was significantly less in the glucan group (0% versus 29%) (p less than 0.05), the mortality rate from sepsis was not statistically different (0% versus 17.6%). Glucan therapy significantly decreased septic morbidity (9.5% versus 49%; p less than 0.05). Serum IL-1 had a greater increase in glucan patients on day 3 after trauma (143.4 +/- 19.3% versus 78.6 +/- 11.7%; p less than 0.05), but there was no difference thereafter. Serum TNF did not vary between groups. Early increase in IL-1 correlated with subsequent skin test conversion to positive. Neither serum IL-1 nor TNF was a reliable indicator of future sepsis. Further clinical trials are indicated to evaluate biologic response modifiers that activate macrophages in the trauma patient. |

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| Rasmussen LT, Seljelid R.<br><br>**Dynamics of blood components and peritoneal fluid during treatment of murine *E.coli* sepsis with beta-1,3-D-polyglucose derivatives. I. Cells.**<br><br>*Scand J Immunol.* 1990 Oct;32(4):321-31.<br><br>PMID: 2237287 [PubMed - indexed for MEDLINE] | Beta-1,3-D-polyglucose derivatives protect mice against otherwise lethal bacterial infections. This protective effect has previously been considered to be mediated through mononuclear phagocytes. We have now investigated the cellular composition in blood and peritoneal fluid after administration of the beta-1,3-D-polyglucose before and after challenge with *Escherichia coli*. In animals treated with beta-1,3-D-polyglucose derivatives, the total white cell number was significantly increased in both blood and peritoneal fluid before and after challenge with *E. coli*. The increased total cell number was mainly the result of raised levels of granulocytes. The effects of beta-1,3-D-polyglucose-derivatized microbeads (GDM) and soluble aminated beta-1,3-D-polyglucose (AG) were similar. Bacterial counts in peripheral blood in GDM- and AG-treated animals increased with 6 h after challenge and approached zero after 24 h. In untreated animals the bacterial counts increased gradually until the animals died after about 12 h. Bacterial counts in peritoneal fluid of GDM- and AG-treated animals declined to zero after 24 h. In untreated animals there was a slight increase in bacterial counts until the animals died after about 12 h. By using radioactive labelling, we localized the bacterial as well as the beta-1,3-D-polyglucose derivatives during the period following injection. Particle-bound beta-1,3-D-polyglucose was recovered mainly in the milky spots of the omentum. A conspicuous number of bacteria were also recovered in the milky spots. The soluble aminated beta-1,3-D-polyglucose was recovered mainly in the liver. However, on a weight basis, the greatest concentration of radioactivity was in the milky spots. |
| Rasmussen LT, Fandrem J, Seljelid R.<br><br>**Dynamics of blood components and peritoneal fluid during treatment of murine *E.coli* sepsis with beta-1,3-D-polyglucose derivatives. II. Interleukin 1, tumour necrosis factor, prostaglandin E2, and leukotriene B4.**<br><br>*Scand J Immunol.* 1990 Oct;32(4):333-40.<br><br>PMID: 2173131 [PubMed - indexed for MEDLINE] | The influences of pretreatment with beta-1,3-D-polyglucose derivatives on levels of cytokines and arachidonic acid metabolites in body fluids in experimental peritonitis in mice are reported. Peritonitis was induced by an intraperitoneal injection of 10(8) live *Escherichia coli*. Pretreated animals survived the infection, untreated animals died about 12 h after inoculation with *E. coli*. Levels of IL-1 in plasma and peritoneal fluid, measured by cytotoxicity assay of the HT-2 cell line, increased significantly during the first 48 h after intraperitoneal treatment with beta-1,3-D-polyglucose-derivatized microbeads (GDM) or soluble, aminated beta-1,3-D-polyglucose (AG). After subsequent challenge with *E. coli*, the levels of IL-1 were significantly lower than in untreated animals. There was no increase in levels of TNF after treatment with GDM or AG, measured by cytotoxicity assay of the WEHI clone 13 cell line. After challenge with *E. coli*, TNF in plasma and peritoneal fluid was significantly lower compared with untreated animals. Both PGE2 and LTB4, measured by radioimmunoassay kits, were increased in peritoneal fluid after treatment with GDM and AG. After challenge with *E. coli*, PGE2 and LTB4 in peritoneal fluid increased to about half the concentration of infected control animals. Intraperitoneal injection of indomethacin to pretreated animals resulted in increased levels of IL-1 and TNF and decreased levels of PGE2 following challenge with *E. coli*. The levels of IL-1 and TNF remained elevated until the animals died after about 12 h. These studies demonstrate that the raised levels of arachidonic acid metabolites after pretreatment with GDM or AG seem to inhibit the otherwise lethal elevation of IL-1 and TNF in body fluids which is seen in untreated animals. |

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| Maheshwari R, Siddiqui MU.<br><br>**Immunoprotection by beta-1,3 glucan antigen combination in *Plasmodium berghei* infection in mice.**<br><br>*Indian J Med Res*. 1989 Nov;89:396-403.<br><br>PMID: 2695459 [PubMed - indexed for MEDLINE] | In an attempt to protect mice against experimental infection with *P. berghei*, mice were immunized against soluble extract of *P. berghei* in combination with beta-1,3 glucan or FCA and also independently. Mice immunized against *P. berghei* antigen-glucan developed well defined cell mediated and humoral immune responses, while mice injected with antigen FCA or antigen alone developed only an antibody response. Antigen-glucan immunization afforded a high degree of immune protection to the host against the challenge with live parasites. |
| Williams DL, Yaeger RG, Pretus HA, Browder IW, McNamee RB, Jones EL.<br><br>**Immunization against Trypanosoma cruzi: adjuvant effect of glucan.**<br><br>*Int J Immunopharmacol.* 1989;11(4):403-10.<br><br>PMID: 2506140 [PubMed - indexed for MEDLINE] | Trypanosoma cruzi, the causative agent of Chagas' disease, infects humans and animals in tropical, subtropical and some temperature regions of the western hemisphere. At present, there is no effective vaccine for T. cruzi infection. Glucan, a beta-1,3 polyglucose biological response modifier, possesses significant adjuvant activity. The present study investigated the adjuvant activity of particulate glucan when combined with a vaccine of glutaraldehyde-killed T. cruzi culture forms. ICR/HSD mice (20 g) were injected s.c. with glutaraldehyde-killed T. cruzi on days 21, 14 and 7 prior to challenge with 50 T. cruzi blood forms. Particulate glucan (1 mg/mouse) was administered s.c. either alone or in conjunction with T. cruzi vaccine. Isovolumetric dextrose served as control. Dextrose, glucan or T. cruzi vaccine as single treatment regimens showed 100% mortality with 20.5, 21.4 and 21.6 day median survival times, respectively. In contrast, glucan administered with T. cruzi vaccine showed an 85% (P less than 0.01) survival at 275 days post-challenge. In addition, the number of T. cruzi observed in the blood of glucan--T. cruzi immunized mice was lower than the appropriate controls. However, immunized mice which survived at 275 days were positive for the presence of T. cruzi by xenodiagnosis. Histopathologic evaluation of glucan--T. cruzi mice revealed no parasites or cardiac pathology, but a mild splenic hyperplasia and inflammation of skeletal muscle were noted. In subsequent studies, mice were immunized with the same regimen of glucan--T. cruzi and challenged with 500 or 5000 T. cruzi. Glucan significantly (P less than 0.05) increased survival as denoted by 60% and 50% survival in the glucan-T. cruzi group vs 0% in controls.(ABSTRACT TRUNCATED AT 250 WORDS) |
| Bowers GJ, Patchen ML, MacVittie TJ, Hirsch EF, Fink MP.<br><br>**Glucan enhances survival in an intraabdominal infection model.**<br><br>*J Surg Res.* 1989 Aug;47(2):183-8.<br><br>PMID: 2755122 [PubMed - indexed for MEDLINE] | The immunomodulator glucan exists in two forms, particulate (glucan-P) and soluble (glucan-F). Both preparations of glucan, either alone or in combination with antibiotic therapy, were evaluated for their ability to augment survival in rats following cecal ligation and puncture (CL/P). Adult male rats were infused once daily for 5 consecutive days with either glucan-P (10 mg/kg), glucan-F (10 mg/kg), or 5% (w/v) dextrose in water. Three days later all rats underwent CL/P. Postoperatively, the rats received (a) no therapy, (b) saline (1 ml subcutaneously every 12 hr) or (c) ampicillin (33 mg/kg subcutaneously every 12 hr) for 7 days. Without any associated pre-or postoperative treatment, CL/P was associated with an 85% 7-day mortality. Neither glucan preparation alone significantly altered this mortality. Administering ampicillin postoperatively decreased the mortality to 53% (P less than 0.001 vs |

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| | untreated controls). When postoperative ampicillin therapy was combined with preoperative glucan treatment, the mortality was reduced even further (26% for glucan-P, 21% for glucan-F; P less than 0.02 vs ampicillin-treated controls). We conclude from these results that (i) neither glucan preparation alone effectively enhances survival following CL/P when using the doses and administration schedule employed herein, (ii) both glucan-P and glucan-F do act synergistically with antibiotics to enhance survival in this rat model of polymicrobial sepsis, and (iii) in this particular model, nontoxic glucan-F is as efficacious as glucan-P. |
| Williams DL, Sherwood ER, Browder IW, McNamee RB, Jones EL, Di Luzio NR.<br><br>**The role of complement in glucan-induced protection against septic shock.**<br><br>*Circ Shock*. 1988 May;25(1):53-60.<br><br>PMID: 3042187 [PubMed - indexed for MEDLINE] | Previous studies from our laboratory have shown that glucan will significantly enhance survival, decrease bacteremia, maintain reticuloendothelial function, and reduce histopathology in a murine model of gram-negative septic shock [1]. The present study was undertaken to evaluate the role of complement in glucan-enhanced protection against septic shock. AKR/J mice, which are congenitally C5-deficient, and ICR/HSD mice that were complement-depleted by treatment with purified cobra venom factor (CVF), were injected IP with glucan (50 mg/kg) on days 5 and 3 prior to IP challenge with 1 X 10(8) *E. coli*. Survival data indicated that glucan (p less than 0.05) increased survival in both C5-deficient and complement-depleted mice. Glucan prophylaxis resulted in a neutrophilic leukocytosis 8 h following E. coli challenge. However, glucan did not alter bone marrow proliferation. We conclude that, 1) glucan's protective effect on survival is not dependent on complement, 2) complement is not required for glucan-induced neutrophilic leukocytosis in this model, and 3) glucan does not enhance bone marrow proliferation in complement-deficient mice. |
| Williams DL, Sherwood ER, Browder IW, McNamee RB, Jones EL, Rakinic J, Di Luzio NR.<br><br>**Effect of glucan on neutrophil dynamics and immune function in *Escherichia coli* peritonitis.**<br><br>*J Surg Res*. 1988 Jan;44(1):54-61.<br><br>PMID: 3275833 [PubMed - indexed for MEDLINE] | Previous studies from our laboratory have demonstrated that glucan, a nonspecific immunomodulator, modifies the course of murine *Escherichia coli* peritonitis. The protective effect of glucan was mediated, in part, by macrophages. In the present study, leukocyte dynamics in the peritoneal cavity and peripheral blood of glucan-treated mice following *E. coli* challenge was examined. Additional studies examined in vitro bone marrow proliferation, as well as phagocytosis and intracellular killing of *E. coli* by neutrophils following glucan administration. ICR/HSD mice were injected ip with glucan (150 mg/kg) or dextrose (5% w/v) on Days 5 and 3 prior to ip challenge with 1 X 10(8) E. coli. Glucan increased (P less than 0.05) total peritoneal neutrophil numbers prior to and following septic challenge. Examination of peripheral blood revealed that ip glucan treatment in *E. coli* peritonitis significantly (P less than 0.001) increased the number of circulating neutrophils. Additionally, neutrophils from glucan-treated mice showed increased phagocytosis of *E. coli* in vitro. Glucan therapy also increased bone marrow proliferation. We conclude that (1) glucan enhances peritoneal neutrophil levels, (2) peripheral blood neutrophils are increased following glucan and *E. coli*, (3) ip glucan increases bone marrow proliferation, and (4) neutrophils from glucan-treated mice showed enhanced phagocytosis of *E. coli* in vitro. Thus, the beneficial effect of glucan is mediated not only by activated macrophages, but also by the neutrophilic leukocyte. |

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| Browder W, Williams D, Sherwood E, McNamee R, Jones E, DiLuzio N.<br><br>**Synergistic effect of nonspecific immunostimulation and antibiotics in experimental peritonitis.**<br><br>*Surgery. 1987* Aug;102(2):206-14.<br><br>PMID: 3303398 [PubMed - indexed for MEDLINE] | To assess the role of combined immunomodulator and antibiotic therapy in sepsis, glucan--a beta 1,3 polyglucose--and gentamicin were administered in a model of murine peritonitis. ICR/HSD mice received one of four treatment regimens: 5% dextrose; gentamicin 0.02 mg intramuscularly (sub-MIC) 2 hours before peritonitis; glucan 0.1 mg intraperitoneally 24 hours before peritonitis; combined glucan-gentamicin treatment. All animals were challenged with 1 X 10(8) *Escherichia coli* intraperitoneally. Long-term survival was significantly enhanced in the combined therapy group (56%, p less than 0.05) when compared with D5W (0%), gentamicin alone (0%), or glucan alone (9%). Macrophage secretory activity, as assayed by interleukin-1 (IL-1) production, was significantly enhanced by combined therapy when compared with the other three treatment groups. Combined therapy significantly reduced *E. coli* bacteremia at 8 hours after inoculation, when compared with the other three groups. Availability of host neutrophils was assessed by peripheral counts and bone marrow proliferation assay. Combined glucan-gentamicin significantly enhanced bone marrow proliferation when compared with the other three groups and this enhancement correlated with increased circulating neutrophils. Combined immunomodulator and antibiotic therapy had synergistic effects on survival in *E. coli* peritonitis. This combined therapy enhanced macrophage secretory activity and bone marrow proliferation. Clinical use of immunomodulators may alter conventional use and dosage of antibiotics. |
| Almdahl SM, Bogwald J, Hoffman J, Sjunneskog C, Seljelid R.<br><br>**The effect of splenectomy on *Escherichia coli* sepsis and its treatment with semisoluble aminated glucan.**<br><br>*Scand J Gastroenterol*. 1987 Apr;22(3):261-7.<br><br>PMID: 3296131 [PubMed - indexed for MEDLINE] | Rats were subjected to sham laparotomy or splenectomy and were challenged with either 0.2 X 10(9) *Escherichia coli* intravenously or 1 X 10(9) *E. coli* intraperitoneally. By means of quantitative blood culturing asplenic animals were shown to have a significantly impaired ability to clear the bacteria in both forms of challenge. Treatment with intraperitoneally injected semisoluble aminated glucan (SAG), known to have strong macrophage-stimulatory properties, compensated completely for the asplenic state. The substance protected against postsplenectomy sepsis both when given before and when given after removal of the spleen. This protective effect of SAG seemed to last at least 3 weeks. |
| Seljelid R, Rasmussen LT, Larm O, Hoffman J.<br><br>**The protective effect of beta 1-3D-glucan-derivatized plastic beads against *Escherichia coli* infection in mice.**<br><br>*Scand J Immunol.* 1987 Jan;25(1):55-60.<br><br>PMID: 3544199 [PubMed - indexed for MEDLINE] | Pretreatment with beta-1,3-D-glucan-derivatized plastic beads conferred strong protection against *Escherichia coli* infection in mice. The protective effect showed a dose-response relationship to the amount of beads injected and was dependent on the time point of the injection relative to the infection with *E. coli*. A similar protection could be obtained in nude mice. Experiments with radioactively labelled bacteria as well as beads indicated a systemic effect of the beads. Macrophages extracted from animals treated with glucan plastic beads appeared highly stimulated. This was also true of cells that did not contain beads and presumably therefore not glucan, which seems to indicate a soluble stimulatory factor. |

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| Seljelid R, Bogwald J, Rasmussen LT, Larm O, Hoffman J, Berge A, Ugelstad J.<br><br>**In vivo activation of mouse macrophages with beta-1,3-D-glucan-derivatized plastic beads.**<br><br>*Scand J Immunol.* 1985 Jun;21(6):601-5.<br><br>PMID: 4023630 [PubMed - indexed for MEDLINE] | Macrophages obtained from animals treated with beta-1,3-D-glucan-derivatized plastic beads were greatly stimulated, as judged by morphology, esterase release, and cytostatic effect on L-929 tumour cells in vitro. The pretreatment of mice with such beads conferred an apparent absolute local resistance to an otherwise lethal pneumococcal infection but had no effect on the growth of intraperitoneal AA ascites sarcoma. Moreover, peritoneal cells from animals pretreated with glucan beads did not protect the animals in a Winn assay. |
| Browder IW, Williams DL, Kitahama A, Di Luzio NR.<br><br>**Modification of post-operative *C. albicans* sepsis by glucan immunostimulation.**<br><br>*Int J Immunopharmacol.* 1984;6(1):19-26.<br><br>PMID: 6724765 [PubMed - indexed for MEDLINE] | Glucan, a beta-1,3 polyglucose, was evaluated for its ability to enhance resistance of post-operative mice to experimentally induced *C. albicans* sepsis. Male C57BL/6J mice were injected i.v. with glucan (0.45 mg/mouse) on days 10,7,4 and 1 prior to midline laparotomy and intravenous challenge with 3 X 10(6) *C. albicans*. The detrimental effect of surgery on survival following *C. albicans* infection was manifested by a 47% survival in the non-surgery-infected group in contrast to 20% in the surgery-infected group. Protection against C. albicans was observed in the glucan-treated groups. The glucan-treated non-operated mice manifested 100% survival while the surgery group had a 73% survival. Glucan significantly enhanced macrophage phagocytic function in control and operated mice. Laparotomy alone did not significantly depress macrophage phagocytosis. Histopathological studies revealed that glucan markedly inhibited the renal pathology associated with *C. albicans* challenge both in the presence and absence of laparotomy. These data indicate that glucan increased survival and reduced renal pathology associated with *C. albicans* challenge in the post-operative period. These observations suggest that Biologic Response Modifiers such as glucan may be effectively employed in patients who are at risk for post-operative infections. |
| Browder W, Rakinic J, McNamee R, Jones E, Williams D, Di Luzio N.<br><br>**Protective effect of nonspecific immunostimulation in postsplenectomy sepsis.**<br><br>*J Surg Res.* 1983 Dec;35(6):474-9.<br><br>PMID: 6656237 [PubMed - indexed for MEDLINE] | The enhanced risk of severe sepsis following splenectomy is now well recognized in both adult and pediatric patients. Prophylactic antibiotics and bacterial vaccines have been utilized with limited success to inhibit the high morbidity and mortality. This study reports the use of glucan, a beta-1,3-polyglucose, as a nonspecific immunostimulant for postsplenectomy pneumococcal sepsis. ICR mice were treated with glucan or glucose (5% w/v) following splenectomy or sham operation. Mice were then challenged with 1 X 10(9) *Streptococcus pneumoniae* intranasally. Glucan significantly increased survival in the splenectomy group (75%) compared to controls (27%). Phagocytic function, as measured by the clearance of 131I-triolein-labeled reticuloendothelial test lipid emulsion, was increased in the glucan group when compared to control glucose animals, both in the presence and absence of pneumococcal infection. Splenectomy alone did not significantly decrease phagocytic function. An increased leukocytosis in response to pneumococcal infection was observed in splenectomized glucan-treated animals. Nonspecific immunostimulation appears to have significant potential as a treatment strategy against postsplenectomy infection. |

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| Williams DL, Browder IW, Di Luzio NR.<br><br>**Immunotherapeutic modification of *Escherichia coli*--induced experimental peritonitis and bacteremia by glucan.**<br><br>*Surgery. 1983* Mar;93(3):448-54.<br><br>PMID: 6338616 [PubMed - indexed for MEDLINE] | Previous data from our laboratory have demonstrated that glucan administration significantly alters the course of a variety of experimentally induced infectious diseases. In view of the increasing incidence of gram-negative infections, studies were initiated to evaluate the effect of intraperitoneal glucan therapy on *Escherichia coli*-induced peritonitis and sepsis. Male ICR/Tex mice were injected intraperitoneally with glucan or dextrose on days 5 and 3 prior to intraperitoneal challenge with 1.0 x 10(8) *E. coli*. Glucan administration resulted in a significant enhancement of survival. Evaluation of the mechanism of protective action of glucan revealed that both the glucan and dextrose control groups showed an equivalent level of blood-borne *E. coli* at early periods. At 6 hours after challenge the glucan group showed a significant decrease in blood-borne *E. coli*. In contrast, the dextrose control group demonstrated progressive bacteremia. A significant depression of phagocytic activity occurred in *E. coli*-infected mice as compared with control mice that were not exposed to the bacterial challenge. The enhancement in phagocytic function observed in glucan-treated control mice was unaltered in *E. coli* challenged, glucan-treated mice. The possible importance of hyperfunctional macrophages in reduction of mortality from *E. coli* sepsis was denoted by methyl palmitate-induced reversal of the glucan hyperfunctional state. Methyl palmitate-treated glucan injected mice were not protected against *E. coli* infection. These data denote that the intraperitoneal administration of glucan significantly modifies the course of *E. coli*-induced peritonitis and bacteremia due, in part, to glucan-induced enhancement of macrophage function. |
| Daniel E. Cramer, Daniel J. Allendorf, Jarek T. Baran, Richard Hansen, Jose Marroquin, Bing Li, Janina Ratajczak, Mariusz Z. Ratajczak, and Jun Yan<br><br>**β-Glucan Enhances Complemented-Mediated Hematopoietic Recovery after Bone Marrow Injury**<br><br>Blood. 15 January 2006. Volume 107, Number 2 | Myelotoxic injury in the bone marrow (BM) as a consequence of total body irradiation (TBI) or granulocyte colony-stimulating factor (G-CSF) mobilization results in the deposition of iC3b on BM stroma (stroma-iC3b). In the present study, we have examined how stroma-iC3b interacts with hematopoietic progenitor cells (HPCs) and the role of complement (C) and complement receptor 3 (CR3) in BM injury/repair. We demonstrate here that stroma-iC3b tethers HPCs via the inserted (I) domain of HPC complement receptor 3 (CR3, CD11b/CD18, Mac-1). Following irradiation, stroma-iC3b was observed in the presence of purified IgM and normal mouse serum (NMS), but not serum from Rag-2$^{-}$/$^{-}$ mice, implicating a role for antibody (Ab) and the classic pathway of C activation. Furthermore, a novel role for soluble yeast β-glucan, a ligand for the CR3 lectin–like domain (LLD), in the priming of CR3□ HPC is suggested. Soluble yeast β-glucan could enhance the proliferation of tethered HPCs, promote leukocyte recovery following sublethal irradiation, and increase the survival of lethally irradiated animals following allogeneic HPC transplantation in a CR3-dependent manner. Taken together, these observations suggest a novel role for C, CR3, and β-glucan in the restoration of hematopoiesis following injury. |

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| Turnbull, J. L., M. L. Patchen, and D. T. Scadden.<br><br>**The polysaccharide, PGG-glucan, enhances human myelopoiesis by direct action independent of and additive to early-acting cytokines.**<br><br>*Acta Haematol.* 1999. 0102:66-71.<br><br>PMID: 10529508 [PubMed - indexed for MEDLINE] | βeta-Glucans stimulate leukocyte anti-infective activity, enhance murine hematopoietic recovery following bone marrow injury and mobilize murine progenitor cells from bone marrow. This study evaluated the in vitro hematopoietic potential of the beta-glucan, PGG-glucan, on human bone marrow mononuclear cells (BMMC) and CD34+ BMMC compared with protein cytokines. In the presence of submaximal concentrations of recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF; 0.5 ng/ml), PGG-glucan significantly increased BMMC myeloid colony formation comparable to the increase observed with either interleukin-3 (rhIL-3) or stem cell factor (rhSCF). Moreover, the addition of PGG-glucan to cultures containing GM-CSF + IL-3 or GM-CSF + SCF significantly augmented granulocyte-macrophage colony production above baseline, demonstrating that PGG-glucan acts independently of those early-acting cytokines and can enhance their activity in an additive manner. Anti-PGG-glucan monoclonal antibody specifically abrogated the growth-enhancing effect of added PGG-glucan in a saturable manner and other control carbohydrate polymers failed to affect colony formation. Further, PGG-glucan was not associated with induction of IL-6, GM-CSF production and removal of accessory cells by CD34+ cell isolation did not alter the PGG-glucan effect. These data demonstrate that PGG-glucan acts on committed myeloid progenitors to enhance human hematopoietic activity by a mechanism of direct action independent of IL-3 or SCF and independent of secondary cytokine stimulation. |
| Patchen, M. L., T. Vaudrain, H. Correira, T. Martin, and D. Reese.<br><br>**In vitro and in vivo hematopoietic activities of Betafectin PGG-glucan.**<br><br>*Exp. Hematol.* 1998. 26:1247-1254.<br><br>PMID: 9845381 [PubMed - indexed for MEDLINE] | Betafectin PGG-glucan is a novel beta-(1,3)glucan that has broad-spectrum anti-infective activities without cytokine induction. Here we report that PGG-glucan also has both in vitro and in vivo hematopoietic activities. In vitro studies with bone marrow target cells from the C3H/HeN mouse revealed that although PGG-glucan alone had no direct effect on hematopoietic colony-forming cell (CFC) growth, when combined with granulocyte colony-stimulating factor (CSF) or granulocyte-macrophage CSF, it increased CFC numbers 1.5- to 2.0-fold over those obtained with CSFs alone. Bone marrow cells cultured for high-proliferative-potential CFCs in the presence of interleukin (IL)-1, IL-3, macrophage CSF, and stem cell factor (SCF), or cultured for erythroid burst-forming units in the presence of IL-3, SCF, and erythropoietin, also exhibited enhanced growth in the presence of PGG-glucan. The synergistic effect of PGG-glucan was specific and could be abrogated by anti-PGG-glucan antibody. The ability of PGG-glucan to modulate hematopoiesis in vivo was evaluated in myelosuppressed rodents and primates. C3H/HeN female mice were intravenously administered saline solution or PGG-glucan (0.5 mg/kg) 24 hours before the intraperitoneal administration of cyclophosphamide (200 mg/kg), and the recovery of bone marrow cellularity and granulocyte-macrophage progenitor cells was evaluated on days 4 and 8 after cyclophosphamide treatment. At both time points, enhanced hematopoietic recovery was observed in PGG-glucan-treated mice compared with saline-treated control mice. In a final series of in vivo experiments, we evaluated the ability of therapeutically administered PGG-glucan to enhance hematopoietic recovery in cyclophosphamide-treated cynomolgus monkeys. Monkeys received intravenous infusions of cyclophosphamide (55 mg/kg) on days 1 and 2, followed on days 3 and 10 by intravenous infusion of PGG-glucan (0.5, 1.0, or 2.0 mg/kg). Compared with those in saline-treated monkeys, accelerated white blood cell recovery and a reduction in the median duration of neutropenia were observed in PGG-glucan-treated monkeys. These studies illustrate that PGG-glucan has both in vitro and in vivo hematopoietic activities and that this agent may be useful in the prevention and/or treatment of chemotherapy-associated myelosuppression. |

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| Hofer M, Pospisil M.<br><br>**Glucan as stimulator of hematopoiesis in normal and gamma-irradiated mice. A survey of the authors' results.**<br><br>*Int J Immunopharmacol.* 1997 Sep-Oct;19(9-10):607-9.<br><br>PMID: 9637361 [PubMed - indexed for MEDLINE] | Glucan, a beta-1,3-linked polyglucose derived from the yeast *Saccharomyces cerevisiae*, is a broad spectrum enhancer of host defense mechanisms stimulating humoral and cell-mediated immunity. On the basis of these features, glucan has been tested by the authors' research group in experiments on gamma-irradiated mice. Two glucan forms, particulate and soluble, have been studied. Attention has been focused on various application regimens in relation to the time of irradiation (pre- or postirradiation application), the possibilities of using glucan in various radiation regimens (single or repeated irradiation), combined pharmacological therapy (joint administration of glucan with cystamine or inhibitors of prostaglandin synthesis), and on the negative side effects of therapy with glucan. Some studies included also experiments on unirradiated mice. The results have demonstrated the ability of glucan to influence positively the course of the acute radiation disease. Stimulation of hematopoiesis has been found to be the most important mechanism of glucan's radioprotective effects. In this communication, the results of 11 full-length articles are summarized and discussed. |
| Patchen ML, Brook I, Elliott TB, Jackson WE.<br><br>**Adverse effects of pefloxacin in irradiated C3H/HeN mice: correction with glucan therapy.**<br><br>*Antimicrob Agents Chemother*. 1993 Sep;37(9):1882-9.<br><br>PMID: 8239601 [PubMed - indexed for MEDLINE] | Opportunistic bacterial infections are the predominant cause of death following myelosuppressive radiation exposure. When used alone, a variety of immunomodulators and antibiotics have been reported to reduce radiation-induced death. In these studies, the combined therapeutic effects of the immunomodulator glucan and the quinolone antibiotic pefloxacin were evaluated for survival-enhancing effects in myelosuppressed C3H/HeN mice. Mice were exposed to 7.9 Gy of whole-body 60Co radiation and treated with saline, glucan (250 mg/kg of body weight intravenously, 1 h after irradiation), pefloxacin (64 mg/kg/day orally, days 3 to 24 after irradiation), or glucan plus pefloxacin. Survival 30 days after irradiation in mice receiving these respective treatments was 25, 48, 7, and 85%. Evaluation of granulocyte-macrophage progenitor cell (GM-CFC) recovery in mice receiving these treatments revealed that, compared with recovery in saline-treated mice, glucan stimulated GM-CFC recovery, pefloxacin suppressed GM-CFC recovery, and glucan administered in combination with pefloxacin could override pefloxacin's hemopoietic suppressive effect. |
| Baker WH, Nold JB, Patchen ML, Jackson WE.<br><br>**Histopathologic effects of soluble glucan and WR-2721, independently and combined in C3H/HeN mice.**<br><br>*Proc Soc Exp Biol Med*. 1992 Nov;201(2):180-91.<br><br>PMID: 1329111 [PubMed - indexed for MEDLINE] | Soluble glucan, an immunomodulator, and Walter Reed (WR)-2721, a radioprotectant, increase postirradiation survival when administered before and after exposure, respectively. Combined, these agents act synergistically through WR-2721's ability to spare hematopoietic stem/progenitor cells from radiation injury and glucan's ability to subsequently stimulate spared cells to proliferate. In this study, the histopathologic effects of WR-2721 (200 mg/kg, ip) and glucan (250 mg/kg, iv), at doses capable of increasing survival in lethally irradiated mice, were evaluated in unirradiated and irradiated female C3H/HeN mice. After treatment, whole body weights and wet organ weights of liver, spleen, and kidney, as well as gross and histologic changes in these and other tissues, were monitored on Days 1, 4, 7, 11, 15, 21, and 28. Morphometric studies of splenic white and red pulps were also performed. Soluble glucan, with or without WR-2721, in unirradiated groups, was associated with splenomegaly, transient morphometrically determined perturbations of white and red pulp areas, and histologic alterations of white pulp. In irradiated mice, splenic weight loss was initially dampened in glucan groups and accompanied by morphologic and histologic changes similar to those seen in unirradiated counterparts. The subsequent rebound of splenic parameters in irradiated mice was limited to WR-2721-treated mice and was associated with hematopoietic reconstitution. Glucan, with or without WR-2721, in unirradiated groups was associated with transient hepatomegaly and associated histologic changes. Similar changes in irradiated animals were seen only in the combined treatment group. |

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| Patchen ML, MacVittie TJ, Solberg BD, D'Alesandro MM, Brook I.<br><br>**Radioprotection by polysaccharides alone and in combination with aminothiols.**<br><br>*Adv Space Res.* 1992;12(2-3):233-48.<br><br>PMID: 11537014 [PubMed - indexed for MEDLINE] | We demonstrated that glucan, a beta-1,3 polysaccharide immunomodulator, enhances survival of mice when administered before radiation exposure. Glucan's prophylactic survival-enhancing effects are mediated by several mechanisms including (1) increasing macrophage-mediated resistance to potentially lethal postirradiation opportunistic infections, (2) increasing the D(o) of hematopoietic progenitor cells, and (3) accelerating hematopoietic reconstitution. In addition, even when administered shortly after some otherwise lethal doses of radiation, glucan increases survival. Glucan's therapeutic survival-enhancing effects are also mediated through its ability to enhance macrophage function and to accelerate hematopoietic reconstitution; glucan's therapeutic potential, however, is ultimately dependent on the survival of a critical number of hematopoietic stem cells capable of responding to glucan's stimulatory effects. Preirradiation administration of the traditional aminothiol radioprotectants WR-2721 and WR-3689 has been previously demonstrated to be an extremely effective means to increase hematopoietic stem cell survival. Therapeutic glucan treatment administered in combination with preirradiation WR-2721 or WR-3689 treatment synergistically increases both hematopoietic reconstitution and survival. Such combined modality treatments offer new promise in treating acute radiation injury. |
| Patchen ML, MacVittie TJ, Solberg BD, Souza LM.<br><br>**Survival enhancement and hemopoietic regeneration following radiation exposure: therapeutic approach using glucan and granulocyte colony-stimulating factor.**<br><br>*Exp Hematol*. 1990 Oct;18(9):1042-8.<br><br>PMID: 1697806 [PubMed - indexed for MEDLINE] | C3H/HeN female mice were exposed to wholebody cobalt-60 radiation and administered soluble glucan (5 mg i.v. at 1 h following exposure), recombinant human granulocyte colony-stimulating factor (G-CSF; 2.5 micrograms/day s.c., days 3-12 following exposure), or both agents. Treatments were evaluated for their ability to enhance hemopoietic regeneration, and to increase survival after radiation-induced myelosuppression. Both glucan and G-CSF enhanced hemopoietic regeneration alone; however, greater effects were observed in mice receiving both agents. For example, on day 17 following a sublethal 6.5-Gy radiation exposure, mice treated with saline, G-CSF, glucan, or both agents, respectively, exhibited 36%, 65%, 50%, and 78% of normal bone marrow cellularity, and 84%, 175%, 152%, and 212% of normal splenic cellularity. At this same time, granulocyte-macrophage colony-forming cell (GM-CFC) values in saline, G-CSF, glucan, or combination-treated mice, respectively, were 9%, 46%, 26%, and 57% of normal bone marrow values, and 57%, 937%, 364%, and 1477% of normal splenic values. Endogenous spleen colony formation was also increased in all treatment groups, with combination-treated mice exhibiting the greatest effects. Likewise, although both glucan and G-CSF alone enhanced survival following an 8-Gy radiation exposure, greatest survival was observed in mice treated with both agents. These studies suggest that glucan, a macrophage activator, can synergize with G-CSF to further accelerate hemopoietic regeneration and increase survival following radiation-induced myelosuppression. |
| Patchen ML, MacVittie TJ, Weiss JF.<br><br>**Combined modality radioprotection: the use of glucan and selenium with WR-2721.**<br><br>*Int J Radiat Oncol Biol Phys*. 1990 May;18(5):1069-75.<br><br>PMID: 2161407 [PubMed - indexed for MEDLINE] | Glucan, WR-2721, and selenium, three agents with distinct radioprotective mechanisms, were evaluated in C3H/HeN mice for survival-enhancing and hemopoietic-regenerating effects when administered alone or in combinations before exposure to 60Co radiation. At LD50/30 radiation doses (radiation doses lethal for 50% of mice within 30 days postexposure), dose reduction factors of 1.21, 1.02, 1.37, 1.51, and 1.66 were obtained following glucan (75 mg/kg i.v., -20 hr), selenium (0.8 mg/kg, i.p., -20 hr), WR-2721 (200 mg/kg, i.p., -30 min), glucan + WR-2721, and glucan + selenium + WR-2721 treatments, respectively. All treatments increased numbers of hemopoietic stem cells as measured by the day 12 endogenous spleen colony-forming unit (E-CFU) assay; the most significant E-CFU effects, however, were observed following glucan + WR-2721 and glucan + selenium + WR-2721 treatments. Combined modality treatments were also more effective than single-agent treatments at accelerating bone marrow and splenic granulocyte-macrophage colony-forming cell (GM-CFC) regeneration. These results demonstrate the value of multiple-agent radioprotectants. PMID: 2161407 [PubMed - indexed for MEDLINE] |

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| Patchen ML, MacVittie TJ, Jackson WE.<br><br>**Postirradiation glucan administration enhances the radioprotective effects of WR-2721.**<br><br>*Radiat Res.* 1989 Jan;117(1):59-69.<br><br>PMID: 2536480 [PubMed - indexed for MEDLINE] | Based on murine survival studies, endogenous hemopoietic spleen colony formation (E-CFU), and recovery of bone marrow and splenic granulocyte-macrophage colony-forming cells (GM-CFC), it was demonstrated that the postirradiation administration of glucan, an immunomodulator and hemopoietic stimulant, enhances the radioprotective effects of WR-2721. LD50/30 dose reduction factors for mice treated with WR-2721 (200 mg/kg approximately 30 min before irradiation), glucan (250 mg/kg approximately 1 h after irradiation), or both agents were 1.37, 1.08, and 1.52, respectively. Enhanced survival in mice treated with both agents appeared to be due in part to glucan's ability to accelerate hemopoietic regeneration from stem cells initially protected from radiation-induced lethality by WR-2721. Following a 10-Gy radiation exposure, E-CFU numbers in mice treated with saline, WR-2721, glucan, or both WR-2721 and glucan were 0.05 +/- 0.03, 6.70 +/- 1.05, 0.95 +/- 0.24, and 33.90 +/- 2.96, respectively. Similarly, bone marrow and splenic GM-CFC numbers were greater in mice treated with both WR-2721 and glucan than in mice treated with either agent alone. These results demonstrated at least additive radioprotective effects when mice were given WR-2721 prior to irradiation and glucan following irradiation. These effects appeared to depend on the sequential cell protection mediated by WR-2721 and hemopoietic repopulation mediated by glucan. |
| Patchen ML, Chirigos MA, Brook I.<br><br>**Use of glucan and other immunopharmacological agents in the prevention and treatment of acute radiation injuries.**<br><br>*Fundam Appl Toxicol.* 1988 Nov;11(4):573-4. No abstract available.<br><br>PMID: 3229582 [PubMed - indexed for MEDLINE] | N/A |
| Patchen ML, D'Alesandro MM, Chirigos MA, Weiss JF.<br><br>**Radioprotection by biological response modifiers alone and in combination with WR-2721.**<br><br>*Pharmacol Ther.* 1988;39(1-3):247-54. Review. No abstract available.<br><br>PMID: 2849129 [PubMed - indexed for MEDLINE] | N/A |

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| Patchen ML, D'Alesandro MM, Brook I, Blakely WF, MacVittie TJ.<br><br>**Glucan: mechanisms involved in its "radioprotective" effect.**<br><br>*J Leukoc Biol.* 1987 Aug;42(2):95-105.<br><br>PMID: 3036990 [PubMed - indexed for MEDLINE] | It has generally been accepted that most biologically derived agents that are radioprotective in the hemopoietic-syndrome dose range (eg, endotoxin, Bacillus Calmette Guerin, Corynebacterium parvum, etc) exert their beneficial properties by enhancing hemopoietic recovery and hence, by regenerating the host's ability to resist life-threatening opportunistic infections. However, using glucan as a hemopoietic stimulant/radioprotectant, we have demonstrated that host resistance to opportunistic infection is enhanced in these mice even prior to the detection of significant hemopoietic regeneration. This early enhanced resistance to microbial invasion in glucan-treated irradiated mice could be correlated with enhanced and/or prolonged macrophage (but not granulocyte) function. These results suggest that early after irradiation glucan may mediate its radioprotection by enhancing resistance to microbial invasion via mechanisms not necessarily predicated on hemopoietic recovery. In addition, preliminary evidence suggests that glucan can also function as an effective free-radical scavenger. Because macrophages have been shown to selectively phagocytize and sequester glucan, the possibility that these specific cells may be protected by virtue of glucan's scavenging ability is also suggested. |
| Patchen ML, MacVittie TJ.<br><br>**Hemopoietic effects of intravenous soluble glucan administration.**<br><br>*J Immunopharmacol.* 1986;8(3):407-25.<br><br>PMID: 3760593 [PubMed - indexed for MEDLINE] | A soluble form of the reticuloendothelial- and immune modulating agent glucan (glucan-F) has been evaluated for its effects on hemopoiesis. A single 5.0 mg intravenous injection of glucan-F into C3H/HeN mice increased peripheral white blood cellularity, bone marrow and splenic cellularity, bone marrow and splenic granulocyte-macrophage progenitor cell numbers (GM-CFC), and splenic pluripotent stem cell (CFU-s) and erythroid progenitor cell (CFU-e) numbers. Serum levels of granulocyte-macrophage colony stimulating activity (CSA) were also elevated following glucan-F administration. These hemopoietic responses correlate well with those previously shown to be induced by intravenous administration of particulate glucan (glucan-P). In contrast to glucan-P, however, intravenous glucan-F administration has been shown not to induce granuloma formation and severe hepatosplenomegaly, thus the potential clinical use of glucan-F as a hemopoietic stimulant is more likely than that of glucan-P. |
| Patchen ML, MacVittie TJ, Brook I.<br><br>**Glucan-induced hemopoietic and immune stimulation: therapeutic effects in sublethally and lethally irradiated mice.**<br><br>*Methods Find Exp Clin Pharmacol*. 1986 Mar;8(3):151-5.<br><br>PMID: 3713378 [PubMed - indexed for MEDLINE] | The hemopoietic effects of glucan, a beta 1,3 polyglycan biological response modifier, were assayed in normal and irradiated mice. In normal mice, glucan administration increased the content of bone marrow and splenic transplantable pluripotent hemopoietic stem cells (CFU-s), committed granulocyte-macrophage progenitor cells (GM-CFC), and pure macrophage progenitor cells (M-CFC). In mice partially hemopoietic depleted by exposure to 6.5 Gy of 60Co irradiation glucan increased the number of endogenous pluripotent hemopoietic stem cells (E-CFU). The most pronounced effects were observed when glucan was administered 1 day before irradiation. In addition, the administration of glucan 1 day before lethal (9.0 Gy) irradiation-enhanced survival. The enhanced survival in glucan-treated mice in part appeared to be mediated by an enhanced resistance to the surgence of enteric opportunistic pathogens that occurs following radiation-induced hemopoietic and immune depression. |

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| Patchen ML, MacVittie TJ.<br><br>**Comparative effects of soluble and particulate glucans on survival in irradiated mice.**<br><br>*J Biol Response Mod.* 1986 Feb;5(1):45-60.<br><br>PMID: 3958754 [PubMed - indexed for MEDLINE] | The survival-enhancing capabilities of particulate (P) and soluble (F) glucan, a B-1,3 polyglycan biological response modifier, were assayed in 60Co irradiated mice. Although glucan-P was slightly more effective than glucan-F, both glucans significantly enhanced survival in otherwise lethally irradiated (9.0-11.0 Gy) C3H/HeN mice. Following 9.0 Gy, 60% of the glucan-P treated and 53% of the glucan-F treated mice exhibited long-term survival as opposed to 0% of the radiation control mice. The survival-enhancing effects of glucan-P and glucan-F decreased as the radiation dose increased to 11.0 Gy. At higher radiation doses (e.g., 12.0 Gy) neither glucan preparation was capable of enhancing survival. Both glucan-P and glucan-F enhanced the recovery of peripheral blood white cell numbers, platelet numbers, and hematocrit values. In addition, both agents increased endogenous pluripotent hemopoietic stem cell numbers in sublethally irradiated mice. Taken together, these results demonstrate that both glucan-P and glucan-F can significantly enhance survival in lethally irradiated mice. However, these agents appear to function specifically by enhancing hemopoietic recovery and are not effective at radiation does also known to induce gastrointestinal damage. |
| Patchen ML, MacVittie TJ.<br><br>**Stimulated hemopoiesis and enhanced survival following glucan treatment in sublethally and lethally irradiated mice.**<br><br>*Int J Immunopharmacol.* 1985;7(6): 923-32.<br><br>PMID: 4077349 [PubMed - indexed for MEDLINE] | Hemopoietic effects of the reticuloendothelial agent glucan were assayed in normal mice and in mice hemopoietically depleted by exposure to 60Co radiation. In normal mice, glucan administration increased the content of bone marrow and splenic transplantable pluripotent hemopoietic stem cells (CFU-s), committed granulocyte-macrophage progenitor cells (GM-CFC), and pure macrophage progenitor cells (M-CFC). Erythroid progenitor cells (CFU-e) were increased only in the spleen. In sublethally irradiated mice (650 rads), glucan increased the number of endogenous pluripotent hemopoietic stem cells (E-CFU) when administered either before or after irradiation. The most pronounced effects were observed when glucan was administered 1 day before, 1 h before, or 1 h after irradiation. In addition, the administration of glucan before lethal irradiation (900 rads) enhanced survival. The most significant results were seen when glucan was aministered 1 day prior to irradiation. The possibility of using agents such as glucan to enhance hemopoietic reconstitution and prevent septicemia following chemotherapy and/or radiotherapy is discussed. |
| Patchen ML, DiLuzio NR, Jacques P, MacVittie TJ.<br><br>**Soluble polyglycans enhance recovery from cobalt-60--induced hemopoietic injury.**<br><br>*J Biol Response Mod.* 1984 Dec;3(6):627-33.<br><br>PMID: 6512563 [PubMed - indexed for MEDLINE] | Six soluble polyglycans (glucan-C, glucan-F, glucan-S, krestin, lentinan, and schizophyllan), two soluble polymannans (mannan-A and mannan-R), and one soluble polyfructan (levan) were assayed for their ability to enhance hemopoietic recovery in C3H/HeN mice when administered either 1 h before or 1 h after a 6.5-Gy dose of cobalt-60 radiation. Hemopoietic recovery was measured by the endogenous spleen colony assay and was compared with recovery in both radiation control mice and irradiated mice treated with glucan-P (a particulate polyglycan previously shown to enhance recovery from radiation-induced hemopoietic injury). Compared with radiation controls, when administered before irradiation, mannan-A, glucan-F, and glucan-S enhanced endogenous colony formation 4.2-5.1-fold (equivalent to glucan-P), and levan and schizophyllan approximately 2.7-fold. Lentinan, krestin, mannan-R, and glucan-C did not enhance hemopoietic recovery above radiation controls under these conditions. When polyglycan administration was delayed until after irradiation, endogenous colony formation was enhanced 3.0-3.9-fold by mannan-A, schizophyllan, glucan-S, krestin, and glucan-F (at least comparable with glucan-P) but not at all by mannan-R, levan, lentinan, or glucan-C. |

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| Patchen ML, MacVittie TJ, Wathen LM.<br><br>**Effects of pre- and post-irradiation glucan treatment on pluripotent stem cells, granulocyte, macrophage and erythroid progenitor cells, and hemopoietic stromal cells.**<br><br>*Experientia*. 1984 Nov 15;40(11): 1240-4.<br><br>PMID: 6500009 [PubMed - indexed for MEDLINE] | Glucan, a beta-1,3 polyglucose, was administered to mice either 1 h before or 1 h after a 650 rad exposure to cobalt-60 radiation. Compared to radiation controls, glucan-treated mice consistently exhibited a more rapid recovery of pluripotent stem cells and committed granulocyte, macrophage, and erythroid progenitor cells. This may partially explain the mechanism by which glucan also enhances survival in otherwise lethally irradiated mice. |
| Delatte SJ, Evans J, Hebra A, Adamson W, Othersen HB, Tagge EP.<br><br>**Effectiveness of beta-glucan collagen for treatment of partial-thickness burns in children.**<br><br>J Pediatr Surg. 2001 Jan;36(1):113-8.<br><br>PMID: 11150448 [PubMed - indexed for MEDLINE] | **Background/Purpose**: Beta glucan collagen matrix (BGC), which combines the carbohydrate beta-glucan with collagen, has been used as a temporary coverage for adult partial thickness burns with reported good results. Observed advantages of BGC coverage include reduction of pain, improved healing, and better scar appearance. Potentially even more important in children is the elimination of painful daily dressing changes to the burned epithelial surface, as well as decreased fluid loss. This report details the authors' 2-year experience with BGC in a pediatric burn center.<br><br>**Methods**: Retrospective chart review of 225 consecutive pediatric patients treated at our institution between 1997 and 1999 identified 43 patients (19%) with suspected partial thickness burns treated with BGC as the primary wound dressing. BGC was applied to a debrided burn wound and secured with steri-strips, kerlix, and an ace wrap. After 24 hours, adherence of the BGC was confirmed and then left open to air.<br><br>**Results**: The most common cause of burn injury was scald (61%), followed by flame (37%), and contact (2%). The average age of patients was 5.5 years (range, 6 weeks to 16 years) and mean percent total body surface area burned was 9.3% (1% to 35%). Thirty-four patients (79%) had the BGC remain intact while the wound healed underneath, with excellent cosmetic results, minimal analgesic requirements, and no need for repetitive dressing changes. Nine patients (21%) had the BGC removed before wound healing: 6 patients lost the BGC because of progression of the burn to full thickness, 2 had BGC nonadherence over a joint, and 1 had an unexplained nonadherence.<br><br>**Conclusions**: Partial-thickness burns in children can be effectively treated with BGC with good results, even in infants and toddlers. BGC markedly simplifies wound care for the patient and family and seems to significantly decrease postinjury pain. |
| Zulli, F. ; Suter, F.; Biltz, H.; Nissen, H. P.<br><br>**Improving skin function with CM-glucan, a biological response modifier from yeast.**<br><br>International Journal of Cosmetic Science 1998; VOL 20; ISSUE 2; pp. 79-86. | Preparations from yeast have been used for a long time for cosmetic and pharmaceutical purposes. Studies have identified glucan from the cell wall of baker's yeast as an immunologically active agent. Glucan is a poly beta-(1-3)-linked glucopyranose of high molecular weight and belongs to the class of compounds known as biological response modifiers. Glucan preparations are involved in the activation of the body's natural defence mechanisms and in the acceleration of the skin's wound healing processes. In the skin, Langerhans' cells and keratinocytes are the immunologically competent cells. Recent studies indicate that UV irradiation can deplete the number and viability of these cells (immunosuppression). The use of non-specific immune-stimulators, such as glucan, is a new approach for improving the function of stressed skin. We have developed a process to modify pure glucan from baker's yeast to carboxymethyl glucan (CM-glucan), a water soluble product suitable for topical formulations. The functional properties of this new compound have been investigated in vitro and in vivo. Cell culture experiments showed that CM-glucan protects skin cells against |

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| | the depletion of antioxidant molecules upon UV-A irradiation and promotes the growth of keratinocytes. In placebo-controlled studies with healthy volunteers, the pretreatment of skin with CM-glucan offered substantial protection against skin damage caused by a detergent challenge or UV-A irradiation. In addition, CM-glucan enhanced the renewal rate of the stratum corneum. |
| McCauley LK, Somerman MJ.<br><br>**Biologic modifiers in periodontal regeneration.**<br><br>Dent Clin North Am. 1998 Apr;42(2):361-87. Review.<br><br>PMID: 9597341 [PubMed - indexed for MEDLINE] | The specific objective of this article was to update the reader on biologic modifiers being used or suggested for use in therapies directed at regenerating periodontal tissues. As indicated from the studies presented here, many of these biologic modifiers have significant influences on cell behavior and show great promise for use in regenerative therapies. As discussed here, however, additional investigations are required both at the molecular level and at the clinical level to improve the predictability of regenerative therapies. With active investigations directed toward understanding the biology of the healing site, including identifying appropriate cells to target, coupled with designing delivery systems that can control release of agents at the local site, establishing the required environment for regeneration of periodontal tissues should be feasible. |
| Su CH, Sun CS, Juan SW, Hu CH, Ke WT, Sheu MT.<br><br>**Fungal mycelia as the source of chitin and polysaccharides and their applications as skin substitutes**.<br><br>Biomaterials. 1997 Sep;18(17):1169-74.<br><br>PMID: 9259514 [PubMed - indexed for MEDLINE] | A wovenable skin substitute (Sacchachitin) made from the residue of the fruiting body of Ganoderma tsugae was developed in this study. Chemical analysis revealed that the treated residue was a copolymer of beta-1,3-glucan (ca 60%) and N-acetylglucosamine (ca 40%) with a filamental structure of mycelia form, as demonstrated by both optical and scanning electron microscopy. The pulp-like white residue was then woven into thin, porous sheets 7.0 cm in diameter and 0.1-0.2 mm in thickness by filtration and lyophilized for use as a skin substitute. The wound area produced by dissecting rat skin of full thickness was found to almost completely heal on the side covered with Sacchachitin, whereas the control side covered with cotton gauge was around 6.0 cm2 on the 28th day. Furthermore, the wound healing effects of the chitin sheet from crab shell (Beschitin) and Sacchachitin were not found to be significantly different. |
| Portera CA, Love EJ, Memore L, Zhang L, Muller A, Browder W, Williams DL.<br><br>**Effect of macrophage stimulation on collagen biosynthesis in the healing wound.**<br><br>Am Surg. 1997 Feb;63(2):125-31.<br><br>PMID: 9012425 [PubMed - indexed for MEDLINE] | Immunomodulators that enhance macrophage function have been shown to be beneficial in a number of wound-healing models in humans and in experimental animals. The exact mechanism of this improved healing is unclear. To assess the role of collagen biosynthesis, the immunomodulator glucan phosphate was utilized in two murine models of wound healing, i.e., colon anastomosis and full-thickness skin incision. Tensile strength was evaluated using computer-assisted constant velocity tensiometry. Collagen biosynthesis was determined by assaying hydroxyproline content of wound hydrolysates by N-(9-fluorenyl)methoxycarbonyl/o-phthalaldehyde high-performance liquid chromatography. Experimental animals were treated with (1-3)-beta-D-glucan phosphate (250 mg/kg) intravenously 24 hours prior to colon anastomosis or skin incision. A second dose of glucan phosphate was given immediately postoperatively. Control animals received dextrose and water (5% w/v) intravenously. Tensile strength and hydroxyproline content were measured on postoperative Day 3. In the skin wound model, glucan phosphate treatmentincreased ($P < 0.05$) tensile strength by 42 per cent (342.5 +/- 12.2 vs 241.8 +/- 4.8 g), and hydroxyproline content was increased by 23.5 per cent (242.0 +/- 14.4 vs 196.8 +/- 10.5 pmol/microg; $P < 0.05$). In the glucan phosphate group, colon tensile strength was significantly ($P < 0.05$) increased by 34 per cent (34.2 +/- 2.3 g vs 45.8 +/- 2.1 g), and hydroxyproline content was increased by 7 per cent (47.45 +/- 3.31 vs 44.34 +/- 3.74 pmol/microg). These data indicate that macrophage modulation with glucan phosphate will increase tensile strength in experimental colon and skin wounds. In addition, we observed a positive correlation between glucan phosphate treatment, wound tensile strength, and collagen biosynthesis. |

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| Tong DW, Barnetson RS.<br><br>**Beta-1,3-D-glucan gel in the treatment of solar keratoses.**<br><br>Australas J Dermatol. 1996 Aug;37(3):137-8.<br><br>PMID: 8771866 [PubMed - indexed for MEDLINE] | Beta-1,3-D-glucans are yeast-derived carbohydrate polymers which have been shown to be potent immunoresponse modulators which promote the regression of certain tumours. To date there is no published data concerning the efficacy of topical beta-1,3-D-glucan in the treatment of solar keratoses. This randomized double-blind prospective pilot study of 20 patients was performed to investigate the efficacy and skin tolerance of beta-1,3-D-glucan gel versus placebo in the treatment of solar keratoses. The results of this study showed no significant benefit in using beta-1,3-D-glucan gel over placebo in reducing counts of solar keratoses. No adverse effects were reported by any patient at any stage of the trial. |
| Browder W, Williams D, Lucore P, Pretus H, Jones E, McNamee R.<br><br>**Effect of enhanced macrophage function on early wound healing.**<br><br>Surgery. 1988 Aug;104(2):224-30.<br><br>PMID: 3261048 [PubMed - indexed for MEDLINE] | Although the macrophage is important to wound healing, research has focused on its relationship to fibroblast and collagen synthesis. This study was designed to assess effects of enhanced macrophage function on early wound healing, before established collagen synthesis. Sprague-Dawley rats had dorsal incisions after one of three treatment regimens: (1) saline solution, 0.5 ml administered intravenously, (2) intravenous glucan, a macrophage stimulant, 20 mg; (3) topical glucan, 20 mg. Intravenous therapy was administered 24 hours before and after incision. Breaking strength was significantly increased (p less than 0.01) by both intravenous glucan (49.8 +/- 5.5 gm) and topical glucan (59.7 +/- 5.6 gm) on the fourth day after incision, compared with controls (22.0 +/- 2.6 gm). Similar results occurred on the seventh day after incision. Although formalin fixation significantly enhanced breaking strength in fresh control wounds (22.0+/- 2.6 vs 39.5 +/- 2.2 gm), no increase occurred in wounds treated with intravenous glucan (49.8 +/- 5.0 vs 55.3 +/- 6.4 gm), indicating maximal cross-linking of collagen. Collagen synthesis, reflected by tritiated proline uptake, was no different in control versus glucan groups. Supernatants from control or glucan-activated macrophages were injected intraperitoneally or applied topically in the rat model. Activated supernatant, both intraperitoneal and topical, resulted in increased breaking strength on the fourth day after incision. Formalin fixation did not increase breaking strength in the activated supernatant groups. We conclude that enhanced macrophage function increases early wound breaking strength. This effect appears unrelated to collagen synthesis but may be related to increased cross-linking of collagen. Similar effects are seen with activated macrophage secretory products administered intraperitoneally or topically. |
| Kaplan JZ.<br><br>**Acceleration of wound healing by a live yeast cell derivative.**<br><br>Arch Surg. 1984 Sep;119(9):1005-8.<br><br>PMID: 6383269 [PubMed - indexed for MEDLINE] | Acceleration of the normal rate of burn wound healing would serve to decrease the morbidity and possibly the mortality of burn victims. A live yeast cell derivative (LYCD) has previously been reported to stimulate wound epithelialization and this study was designed to evaluate that hypothesis. Twenty-six human skin graft donor sites in nine patients were compared in a double-blind, randomized, single-center inpatient study. Thin donor sites were used as a model for superficial wound healing. Statistically significant earlier angiogenesis and epithelialization occurred in donor sites treated with LYCD ointment as compared with donor sites in the same patients treated simultaneously with ointment base. Stinging pain was noted by seven patients, but in all cases the pain was mild and required no analgesia. |