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Chapter 1 : - Remembering You, Remembering Us

In addition to offering a structured and comprehensive bibliography, this medical reference on mammogram will quickly direct you to resources and reliable information on the Internet, from the essentials to the most advanced areas of research.

Fiscal Year Summary: The chemotherapeutic agent paclitaxel Taxol is widely used for the treatment of many different types of carcinomas. At present, the dose of paclitaxel that can be tolerated by patients is limited primarily by the development of a painful peripheral neuropathy characterized by paresthesias, myalgia and arthralgia. Similar dose-limiting painful neuropathies are produced by other microtubule-disrupting chemotherapeutic drugs, dose-limiting painful neuropathies are produced by other microtubule-disrupting chemotherapeutic drugs, including vincristine therapy, but also increase the effectiveness of their treatment by permitting the use of higher doses of the drugs. We propose a series of experiments to elucidate the cellular mechanisms of paclitaxel- and vincristine-induced painful neuropathy. Specifically, we will establish a model of paclitaxel-induced painful peripheral neuropathy in the rat, and then analyze paclitaxel-induced changes in the excitability of nociceptive nerve fibers in this model. Our interpretation of those data will be greatly enhanced by our extensive knowledge of the effects of vincristine on nerve fiber excitability. Because taxol stabilizes microtubules while vincristine stimulates microtubule depolymerization, comparison of similarities and differences in the effects of the two agents may provide valuable insights into the mechanisms by which microtubule disruption causes nociceptor hyperexcitability. Guided by these *in vivo* electrophysiological analyses, we will employ patch clamp recording of cultured sensory neurons to study the effects of both drugs on specific transduction molecules and ion channels. Finally, we will investigate intracellular second messenger pathways that participate in the production of hyperalgesia and nociceptor hyperexcitability induced by paclitaxel and vincristine. The proposed *in vitro* studies may identify specific molecules to be targeted by new pharmacological strategies to treat chemotherapy-induced neuropathic pain caused by chemotherapy. By improving our understanding of the cellular mechanisms of neuropathic pain, these studies can potentially provide important insights into the pathophysiology and treatment of orofacial neuropathies. Patients with the autosomal recessive disease, Familial Mediterranean fever FMF , suffer periodic, unpredictable attacks of fever associated with severe pain; the pain is localized most commonly in joints arthritis , abdomen peritonitis or chest pleuritis. Occasionally, this disease presents with skin manifestations erysipeloid erythema , pericarditis, vasculitis, or myalgia. In many patients, amyloidosis is a complication, and if untreated, this can be life-threatening. FMF is caused by missense mutations in pyrin, a protein of unknown function expressed in neutrophils, monocytes, eosinophils, dendritic cells, synovial cells and skin and peritoneal fibroblasts. Pyrin expression in these cells is induced by proinflammatory cytokines and by LPS. Thus, it has been speculated that pyrin modulates Studies 7 the inflammatory response. Evolutionary studies of the pyrin molecule indicate that it has been under positive Darwinian selection during evolution of the primates. Moreover, the high frequency of mutant pyrin alleles in several human ethnic groups supports a heterozygote selective advantage for the mutant allele. Indeed, acute phase reactants, important agents of innate immunity, are up-regulated not only in patients but in carriers of mutant alleles. Structural analysis of the pyrin molecule revealed that exon 1 encodes a death-domain related structural motif known as the pyrin domain or PyD that is found in a growing family of proteins involved in inflammation and innate immunity. Identification of pyrin-interacting proteins as well as additional functional studies reveal that pyrin is linked directly to apoptotic and cytoskeletal signaling cascades, and that it modulates cytokine secretion. Experiments described in this proposal are designed to further explore these functions of pyrin and determine the effects of pyrin mutations on apoptosis Aim 1 ; cytoskeletal signaling Aim 2 ; and cytokine production

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Aim 3. Recently identified pyrin isoforms will also be examined in these functional assays, since preliminary studies indicate that the various isoforms may function differently. Such studies could provide clues to understanding of the molecular pathogenesis of FMF, and may reveal new information about inflammatory pathways in general. However, when used at therapeutic doses they produce frequent and sometimes serious side effects, including fever, myalgia, CNS effects and leukopenia, which limit their use. However, as a xenoprotein IFNinterferon is not a suitable candidate for development as a parenteral drug for humans. We have synthesized an analog of human IFNalpha2b, NLVgamma2b, which contains five amino acid substitutions at positions 19, 20, 22, 24 and 27 using residues from the corresponding positions in the IFNinterferon molecule. The in vitro and in vivo data from our SBIR phase I study demonstrated that these substitutions conferred markedly reduced cellular toxicity on the resulting molecule without diminishing its antiviral and antitumor activities. In this phase II project we will advance NLVgamma2b into preclinical development by optimizing expression of this recombinant IFN in yeast, producing pegylated as well as unpegylated preparations and subjecting them to rigorous evaluation in well established animal models. The antiviral, anticancer, immunogenicity and toxicity profiles of NLVgamma2b will be compared with those of commercially available IFNalpha2b. Description adapted from the application: The applicant has proposed two Specific Aims to test his hypothesis. Aim 1 is to explore the effect of methylated and unmethylated CpG motifs of plasmid DNA in the presence or absence of lipid 67 on the production of specific cytokines in human peripheral blood cells PBMCs in vitro, and to test the effect of anti-inflammatory cytokines IL and IL-4 on the production of the specific cytokines. In November in China, an outbreak of atypical pneumonia occurred in which a proportion of cases were very severe or fatal, and a high lethality was seen among elderly patients. The clinical syndrome began with fever, dry cough, myalgia and sore throat and progressed to atypical pneumonia. Extraordinary characteristics of this global epidemic of "Severe Acute Respiratory Syndrome" SARS include the rapid isolation of the etiologic agent a novel coronavirus; SARS-CoV , elucidation of the complete sequence of the viral genome, accelerated development of diagnostic tests, and rapid global exchange of clinical, epidemiologic and microbiologic information via the Internet by scientists and health officials in many countries. Investigators in the USA and Hong Kong were first to isolate from patients the novel coronavirus that is distinct from previously recognized groups of coronavirus. The underlying hypothesis of this research plan is that by appropriate manipulation of attenuated Salmonella enterica serovar Typhi S. Typhi and Shigella live vectors it will be possible to develop a mucosally-administered "prime-boost" vaccination strategy to prevent SARS. We will utilize attenuated S. Typhi or Shigella flexneri 2a live vector vaccine strains to deliver via mucosal immunization a Sindbis eukaryotic DNA replicon encoding the S spike and M membrane glycoproteins and the N nucleocapsid protein of the Urbani strain of the SARS-CoV to prime the immune Studies 9 system to recognize these coronavirus antigens. We will then boost the immune response by mucosally administering proteosomes meningococcal outer membrane protein vesicles to which the same SARS proteins are adsorbed along with a lipopolysaccharide adjuvant. Virus-like Particles and attenuated S. Typhi expressing SARS peptide epitopes will serve as back-up boosting strategies. We will study whether these constructs can elicit the relevant immune responses, first in mice, then in cynomolgus monkeys, and finally in clinical trials in humans the latter under separate funding. The induction of B and T cell memory pools will also be examined in monkeys. This approach aims to mimic the strong and broad immunity elicited by live virus vaccines with the inherent safety factor of not having to use putative attenuated live SARS virus derivatives. If the proposed vaccination strategy can indeed elicit broad, balanced and long-lasting immune responses in cynomolgus monkeys, these studies can be followed by a challenge under respiratory pathogen biosafety level 3 containment to assess the efficacy of the vaccine against wild type SARS-CoV. This search gives you access to fulltext articles. The following is a sample of items found for myalgia in the PubMed Central database: PubMed One of the

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