

mutated KIT protein, whereby the activity level of KIT in the cell is reduced. The invention may prove to be useful for treating diseases such as mastocytosis, gastrointestinal stromal tumors (GIST), mast cell leukemia, myelogenous leukemia, and testicular cancer, all of which are associated with mutations in the c-KIT proto-oncogene.

Recombinant Vaccinia Viruses Expressing IL-15 and Methods of Using the Same

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Vaccinia-based vaccines have a proven record of being effective vaccines in humans as well as in animals. However, accumulating evidence reveals the need for technology to improve the immune responses such vaccines generate.

The present invention discloses recombinant vaccinia viruses capable of expressing interleukin 15 (IL-15), and methods for modulating immune responses using such viruses. This invention shows that by inserting the human IL-15 gene into the vaccinia genome, more effective vaccines can be generated against infectious agents and cancer. Currently, IL-2 has been approved by the FDA for use in the treatment of patients with metastatic renal cell carcinoma or with metastatic melanoma. It has been used as a component of cancer vaccines and in various approaches for the treatment of AIDS. However, administration of IL-2 is associated with activation-induced cell death (AICD), and may lead to death of T-cells that recognize the antigens expressed in the tumor cells. Thus, IL-15 may be a superior agent in the treatment of cancer, or as a component of a vaccine directed towards cancer or infectious agents. Co-delivery of IL-15 with antigens during the immunization process, according to the current invention, leads to induction of CD8+ memory T cells that proliferate more effectively in vivo and persist much longer in the immunized individual in addition to enhancing the levels and persistence of antigen specific antibodies thus providing substantially longer lasting cellular and humoral immunity.

This invention has the potential to be used in a variety of ways, including: (i) An improved, more efficacious vaccine candidate for smallpox, (ii) for incorporation into existing vaccinia based vaccines to enhance and confer superior long lasting immune response to viral and cancer antigens, or (iii) as

a valuable source material for IL-15 production, especially should IL-15 be proven as an alternate of more efficacious cytokine than IL-2.

This research has been described, in part, in *Proc. Natl. Acad. Sci USA* 2003 Mar 18; 100(6):3392-3397.

DNA-Binding Polyamide Drug Conjugates

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Many current anti-cancer drugs have the DNA of cancer cells as their principal target. However, in most instances, the drugs are not selective and are plagued by toxicities, which are frequently dose limiting. The present invention seeks to enhance anti-tumor selectivity and decrease unspecific toxicity. It has been known that various polyamides can target the minor groove of DNA, and rules have been devised to ascertain the sequence-reading properties of the component residues of the polyamide chain. The present invention utilizes sequence-selective polyamide technology together with groups that modify DNA, either by sequence-selective alkylation or strand cleavage. The DNA-modifying moieties that are used for this purpose are novel derivatives based on the cyclopropylbenzindole (CBI) core structure. These compounds alkylate the DNA only when bound into the minor groove, and they provide some DNA-sequence recognizing capability of their own. The DNA-modifying agents are either embedded in the polyamide chain as components of the chain or are located at the termini. These compounds are highly toxic to cancer cells that over-express a targeted DNA sequence (e.g. the c-Myc oncogene promoter sequence) and are much less toxic to non-cancerous tissue. The compounds of the present invention represent a novel method for targeting DNA of cancer cells.

SH2 Domain Binding Inhibitors

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Signal transduction processes underlie the transfer of extracellular information to the interior of the cell

and ultimately to the nucleus. A variety of signal transduction processes are critical for normal cellular homeostasis, with protein-tyrosine kinases (PTKs) playing central roles in many of these pathways. Examples of such PTKs include the PDGF receptor, the FGF receptor, the HGF receptor, members of the EGF receptor family, such as the EGF receptor, erb-B2, erb-B3 and erb-B4, the src kinase family, Fak kinase and the Jak kinase family. Protein-tyrosine phosphorylation that results from the action of PTKs can modulate the activity of certain target enzymes as well as facilitate the formation of specific multi-protein signaling complexes through the actions of homologous protein modules termed Src homology 2 (SH2) domains, which recognize specific phosphotyrosyl containing sequences. A malfunction in this system through tyrosine kinase overexpression and/or deregulation can be manifested by various oncogenic and hyperproliferative disorders, including cancers, inflammation, autoimmune disease, hyperproliferative skin disorders, psoriasis and allergy/asthma, etc. The disclosed compounds, e.g. peptides, preferably, macrocyclic peptides, are Grb2 SH2 domain signaling antagonists with enhanced binding affinity. The claims of the current application are directed to compositions of matter and methods of use which provide for the diagnosis, testing and treatment of the aforementioned disease states.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute; Notice of Closed Meeting

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), notice is hereby given of the following meeting.

The meeting will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., as amended. The grant applications and the discussions could disclose confidential trade secrets or commercial