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### **Transgenic Mouse Model of Human B-cell Neoplasia Based on Myc Insertion into IgH (IgH-Myc<sup>μ</sup>)**

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Some types of cancers are caused by the translocation of genes between two different chromosomes. When a translocation occurs near a highly active promoter, uncontrolled cell growth can be the result if the translocated chromosome piece contains an oncogene. For example, in some types of B cell neoplasias the *Myc* oncogene from chromosome 8 is translocated into the highly transcribed region of the *IgH* locus in chromosome 14.

This invention is a transgenic mouse model that mimics the t(8;14)(q24;q32) translocation commonly found in human sporadic Burkitt's Lymphoma. Specifically, this model has the *Myc* gene inserted into the *IgH* locus just upstream of the constant region C<sub>m</sub>.

Since the *Myc* translocation can occur at various regions within the *IgH* locus, several mouse models of *Myc-IgH* translocations have been developed. Two of these, the IgH-Myc<sup>μ</sup>IgH-Myc<sup>Cα</sup>, have been made available previously. The present specific translocation (IgH-Myc<sup>μ</sup>) animal model will deepen the understanding of the pathogenesis of B-cell neoplasia, uncover new targets for treatment, and serve as a pre-clinical model for innovative intervention approaches.

### **Inducing a T-Cell Response With Recombinant Pestivirus Replicons or Recombinant Pestivirus Replicon-Transfected Dendritic Cells**

Barbara Rehmann *et al.* (NIDDK)  
Serial No. 60/462,165 filed 11 Apr 2003 (DHHS Reference No. E-098-2003); Serial No. 60/463,097 filed 14 Apr 2003 (DHHS Reference No. E-230-2003),  
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Cancer and diseases such as Hepatitis C Virus (HCV), Human Immunodeficiency Virus (HIV), Respiratory Syncytial Virus (RSV), Mycobacterium tuberculosis, Plasmodium falciparum infection, are not effectively prevented by the humoral immune response initiated by standard antigen vaccinations. The neutralizing antibody response created by these types of vaccinations is not effective enough to prevent the progression of the disease. In these cases, a cellular, T-Cell mediated

immune response is a much more effective vaccination strategy.

This invention describes the use of recombinant pestivirus replicons or recombinant pestivirus replicon transfected dendritic cells to induce and/or enhance a T-cell mediated immune response by exploiting the cross-priming ability of endogenous antigen-presenting cells (APCs). These recombinant pestivirus replicons contain an antigen specific to a disease requiring a T-cell response. This antigen is presented to APCs in the lymphatic system by the apoptotic transfected dendritic cells that initiate cross-priming.

This invention generates a stronger immune response than current dendritic cell/APC methods. Because dendritic cells transfected with the recombinant pestivirus replicons survive longer than dendritic cells transfected with other viral replicons, more transfected dendritic cells enter the lymphatic system and undergo apoptosis there. This results in a greater amount of cross-priming and a stronger T-Cell response.

### **Inhibition of Ubiquitin-Mediated Process by UBA Domain Peptides**

Stan Lipkowitz *et al.* (NCI)  
Serial No. 60/464,658 filed 23 Apr 2003 (DHHS Reference No. E-324-2002/0)  
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Ubiquitin is a protein tag that targets cellular proteins for degradation by the multicatalytic protease, the proteasome. A three-component system of ubiquitin activating enzyme (E1), ubiquitin conjugating enzyme (E2), and ubiquitin protein ligase (E3) promotes the covalent attachment of ubiquitin to a protein to be degraded. Of the three components, the E3 component confers the specificity to the ubiquitination.

This invention describes isolated peptides comprising an ubiquitin-associated (UBA) domain that inhibits ubiquitin-mediated protein degradation by binding ubiquitin and polyubiquitin. The series of UBA domain peptides contain a structurally conserved core and a characteristic set of three alpha helices. Specifically, these studies centered on the UBA domain of the proto-oncogene, cbl-b. Expression of the cbl-b UBA-domain peptide in a cell inhibits the degradation of epithelial growth factor (EGFR), murine double minute 2 (Mdm2), and seven in absentia homologue-1 (Siah-1).

UBA domain peptides will be useful in treating conditions associated with an unusually high level of an ubiquitin-mediated process. Defects in the functioning of the ubiquitin/proteasome system can have severe consequences

on biological homeostasis, causing a multitude of pathological conditions. The most obvious treatment options using the UBA-domain peptides could be for cancer, developmental disorders, and inflammatory conditions. In addition, UBA domain peptides can be used to inhibit ubiquitin mediated processes to further the understanding of the cell biological and development roles of these processes.

### **Use of Discoidin Domain Receptor 1 (DDR1) and Agents That Affect the DDR1/Collagen Pathway**

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PCT/US02/39793 filed 11 Dec 2002 (DHHS Reference No. E-083-2002/2-PCT-01),  
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Dendritic cells (DCs) are pivotal antigen-presenting cells for initiation of an immune response. Indeed, dendritic cells provide the basis for the production of an effective immune response to a vaccine, particularly for antigens wherein conventional vaccination is inadequate. DCs are also important in the production of an immune response to tumor antigens.

The present invention discloses methods of using the receptor tyrosine kinase discoidin domain receptor 1 (DDR1) to facilitate the maturation/differentiation of DCs or macrophages. Activating agents of DDR1 may be useful in the induction of a highly potent, mature DCs or highly differentiated macrophages from DC precursors, such as monocytes. Use of this method may enhance the antigen presenting capabilities of the immune system, leading to a more effective overall immune response.

This research is further described in Kamohara *et al.*, *FASEB J.* 10.1096/fj.01-0359fje (published online October 15, 2001) and Matsuyama *et al.*, *FASEB J.* 10.1096/fj.02-0320fje (published online May 8, 2003).

### **Production of Adeno-Associated Viruses in Insect Cells**

Robert Kotin *et al.* (NHLBI)  
Serial No. 09/986,618 filed 09 Nov 2001 (DHHS Reference No. E-325-2001/0); Serial No. 10/216,870 filed 13 Aug 2002 (DHHS Reference No. E-325-2001/1); PCT/US02/35829 filed 08 Nov 2002 (DHHS Reference No. E-325-2001/2),  
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Currently, adeno-associated virus (AAV) is being developed for gene therapy applications. This virus type presents several advantages over alternate vectors for therapeutic gene