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Computer Based Model for the Identification and Characterization of Noncompetitive Inhibitors of the Nicotinic Acetylcholine Receptors and Related Ligand Gated Ion Channels

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NIH announces a method for the rapid determination and characterization of noncompetitive inhibitors for nicotinic acetylcholine receptors (nAChR) and other ligand gated ion channels, to be used in drug discovery and development. Furthermore, inhibitors for AChRs are described, which form a large and chemically heterogeneous group of compounds that block the receptor. Inhibitors of AChRs affect a large variety of physiological processes and many are used for therapeutic purposes in different areas.

Classical methods for the identification and characterization of noncompetitive inhibitors are time consuming and not effective in rapid screening of chemical libraries for potential new drug candidates, nor can they be routinely used in the new drug development process. This invention describes the first computer-based model of the inner lumen of a ligand gated ion channel, as well as unique, previously unidentified and unexpected binding pockets. This method allows for computer simulated structures of the members of chemical libraries to be interacted with the computer-based model of the ligand gated channel and the simulation used to predict and describe the pharmacological importance of the interaction, and to screen for unexpected interactions and toxicities of a drug candidate due to off-target interactions.

Ligand gated ion channels are currently one of the largest targets for drug discovery in the pharmaceutical industry. The Ligand Gated Ion Channel superfamily is separated into the nicotinic receptor superfamily (muscular and neuronal nicotinic, GABA-A and C, glycine and 5-HT₃ receptors), the excitatory amino acid superfamily (glutamate, aspartate and kainate receptors) and the ATP purinergic ligand gated ion channels. These families only differ in the number of transmembrane domains found in each subunit.

This work is partially described in Jozwiak *et al.*, "Displacement and non-linear chromatographic techniques in the investigation of the interaction of noncompetitive inhibitors with an immobilized $\alpha 3\beta 4$ nicotinic acetylcholine receptor liquid chromatographic stationary phase," *Anal. Chem.* 74:4618-4624, 2002.

HeadWave Clinical Coil Designed for Magnetic Resonance Elastography

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The invention is a novel device for measuring the elasticity of cranially encased tissue. The device is a vibrator coil for use in magnetic resonance elastography (MRE). The vibrator coil is applied to the skull of a human patient using a transcranial Doppler monitoring harness and applies mechanical and acoustic waves through the skull. The propagation of the acoustic wave through brain tissue, coupled to phase alteration of voxel isochromats in the presence of applied motion encoding magnetic field gradients permits the measuring of intracranial tissue elasticity.

HTLV-1 p30^{II} and p12^I Proteins as Therapeutic Targets in HTLV-1 Infected Individuals

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The invention provides methods that use the HTLV-1 protein p30^{II} for identification of new drugs able to contain expansion of HTLV-1 virus infected cells and methods of using the identified compounds for treating patients with retroviral infection. The present invention is based upon discovery that viral proteins p30^{II} and p12^I are likely essential for the survival of HTLV-1 infected cells. Working in concert these proteins allow the replication of the infected cells while avoiding immune recognition of the host. The data indicate that both p30^{II} and p12^I can be employed as therapeutic targets in containing replication of HTLV-1 infected cells, which in turn will decrease an HTLV-1 infected patient's chance of developing manifestations associated with HTLV-1 infection, e.g., adult T-cell leukemia/lymphoma and tropical

spastic paraparesis/HTLV-1 associated myelopathy.

Methods and Compositions for Inhibiting HIV-Coreceptor Interactions

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This invention provides peptides that might be potent inhibitors of HIV replication, in both macrophages and T lymphocytes. Specifically, the inventors have identified peptides, from the HIV-1 gp120 envelope protein, that share structural similarities with chemokines and are shown to block "docking" interactions between the HIV-1 envelope protein gp120 and chemokine receptors that function as "coreceptors" for HIV entry on the surface of target cells (macrophages and T lymphocytes). The inventors synthesized two peptides (designated 15K and 15D) based on this information and showed that both were effective in competing with chemokines for binding to CCR5- and CXCR4-expressing cells. These peptides efficiently inhibited infection of human monocyte derived macrophages and peripheral blood mononuclear cells by different strains of HIV. The synthesized peptides also inhibited monocyte chemotaxis stimulated by the chemokine RANTES. Thus, these peptides and other molecules based on their structure can be potentially used as inhibitors of HIV. Moreover, these peptides could also have anti-inflammatory and anti-tumor activity. Further, it has been determined that these peptides are multi-tropic in their effects (blocking HIV interactions with multiple co-receptors) for blocking both T cell tropic (lymphotropic) and macrophage tropic (m-tropic) HIV strains.

3-D Video Image-Based Microscopic Precision Robotic Targeting

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DHHS Reference No. E-162-2000/0
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The invention is a robotic software and hardware system that allows a microscopic object such as a living biological cell to be targeted in 3-D