The major objectives of this research are:

(A) To develop synthetic vaccines for induction of protective immunity against infections with HIV and influenza viruses and shigella bacteria (the cause of dysentery). The following approaches are being studied: a) The use of synthetic peptides containing defined epitopes that lead to neutralizing antibodies and cellular immunity; b) The use of synthetic oligonucleotides encoding such peptides for expressing the epitopes in appropriate vectors; c) Employment of complexes and conjugates containing sero-specific lipo-polysaccharides (LPS).

(B) The immunomodulation of multiple sclerosis and its animal model experimental allergic encephalomyelitis (EAE). To this end, two different strategies are being studied in our laboratory: a) auto-antigen based therapy utilizing a synthetic amino acid copolymer denoted Cop 1, which is immunologically cross reactive with the encephalitogenic myelin basic protein (MBP); and b) T-suppressor lines and clones.

(C) To investigate the involvement of schistosome acetylcholinesterase (AChE) and the phosphatidylinositol-specific phospholipase C (PI-PLC) in signal transduction and the means by which AChE is transported to the parasite surface membrane. The propose of this study is: a) To establish whether AChE can be used as a target for anti-parasite agents that block its vital functions; b) To contribute fundamental research on the molecular structure of invertebrate AChEs and PI-PLC and the organization of the genes encoding them; c) To identify the antigens and epitopes involved in protective immunity.

(D) To elucidate the targeting potential of enzyme-resistant proteins such as streptavidin and avidin that may serve as effective carriers for organ or tissue specific delivery of drugs, radioisotopes, genes and other effector molecules. The purpose of this study is: a) To identify means (tissue epitopes, affinities, physical sequestration etc.) by which these proteins may be targeted to specific organs or tissues; b) To evaluate their potential use as targeting vehicles for various therapeutic and diagnostic agents; c) To investigate antibodies and lectines reactive with common tumor specific epitopes on human cancers for specific immunotargeting of drugs.

Recent Findings:

Synthetic recombinant vaccines - Our main effort is towards the development of influenza vaccine. Using mice as an animal model we demonstrated the efficacy of a vaccine based on recombinant flagella of Salmonella vaccine strain which expresses specific epitopes of the influenza virus. The optimal results were achieved with a combined vaccine expressing three different epitopes - for B-cell, T-cell and CTL-response. Immunization with such a vaccine led to significant reduction of lung virus titer in young and old mice subsequently challenged with several strains of the influenza virus. It also led to a long term, MHC-restricted, protection of mice from a lethal dose challenge. In more recent studies we inserted into the flagellin gene the oligonucleotides encoding for 3 influenza epitopes specific for human HLA - one T-helper epitope and 2 CTL epitopes - and expressed them, as well as the B-cell epitope, in the flagella. The resultant constructs, used in combination, induced an immune response as well as protection in human/mouse radiation chimera. This construct can therefore be developed for a human influenza vaccine.

Our approach for shigella vaccine is based on the strain-specific LPS, complexed to proteosomes, which led to specific immune response and protection after oral or intranasal administration.

Multiple Sclerosis - Work has continued on the elucidation of the mechanism of action of Cop 1 in EAE and multiple sclerosis. A necessary but not sufficient stage in the mechanism of activity of Cop 1 is its efficient and promiscuous binding to almost all MHC class II molecules. In addition, Cop 1 has previously been shown to induce specific suppressor T cell lines and hybridomas. Our recent studies concerning the cytokine profile of these T-suppressor cells have demonstrated secretion of Th2 cytokines after exposure to either Cop 1 or MBP. These results lend support to the “bystander” suppression by Cop 1 of EAE induced by several encephalitogens, e.g. MBP, PLP and MOG, as well as its broad spectrum effect in MS. Recent studies have shown that these cells could be demonstrated in the CNS of mice protected from EAE by Cop 1.
The activity of Cop 1 in suppressing EAE has also been demonstrated by oral administration. This route induces Th2/3 Cop 1 specific suppressor cells similar to those induced by injection of Cop 1. A multi-center clinical trial with oral Cop 1 in exacerbating-remitting type of MS is currently initiated.

*Schistosome Acetylcholinesterase (AChE)* - Acetylcholinesterase (AChE) is an enzyme broadly distributed in many species, including parasites. It occurs in multiple molecular forms which differ in their quaternary structure and mode of anchoring to the cell surface. AChE appears in *S. mansoni* in two principal molecular forms, both globular, with sedimentation coefficients of ca. 6.5S and 8S. Approximately half of the AChE activity of *S. mansoni* is located on the outer surface of the parasite, attached to the tegumental membrane via a covalently attached glycosylphosphatidylinositol anchor. The remainder is located within the parasite, mainly associated with muscle tissue. Whereas the internal enzyme is most likely involved in termination of neurotransmission at cholinergic synapses, the surface enzyme is probably involved in signal transduction. The two forms of AChE differ in their heparin-binding properties, only the internal 8S form of the AChE being retained on a heparin column. Antibodies raised against the internal enzyme are therefore unlikely to be effective in treating the parasitic disease. AChE is thus a functional protein, involved in multi-faceted activities, which can serve as a suitable candidate for diagnostic purposes, vaccine development and drug design.

**Targeting via streptavidin and avidin** - These two proteins were previously characterized as being highly resistant to enzymatic degradation. In addition, both avidin and streptavidin are equipped with extremely efficient binding site for biotin or for any biotinylated compound, which is a major advantage in the targeting process. Bio-distribution of radiolabeled streptavidin showed high and prolonged levels (3-4 days) of biotin-independent accumulation in the kidney (70-80%) of tissue at 24h as compared to less than 5%/g in other organs. Recent studies showed that both streptavidin and avidin can be targeted to different tissues or organs following their chemical modification with tissue specific markers. Consequently, after TNP modification for example, both proteins could target to the liver, as such or when carrying chemotherapeutic agents such as 5-fluorouridine and cisplatin attached to a biotinyl-dextran carrier, resulting in high and prolonged drug levels in the liver tissue. This approach may lead to a new efficient means for organ or tissue targeting.

**Selected Publications (out of 43)**