*Graduate Studies*

**Department of Physiology**
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# Variations on the Theme of Molecular Complementarity

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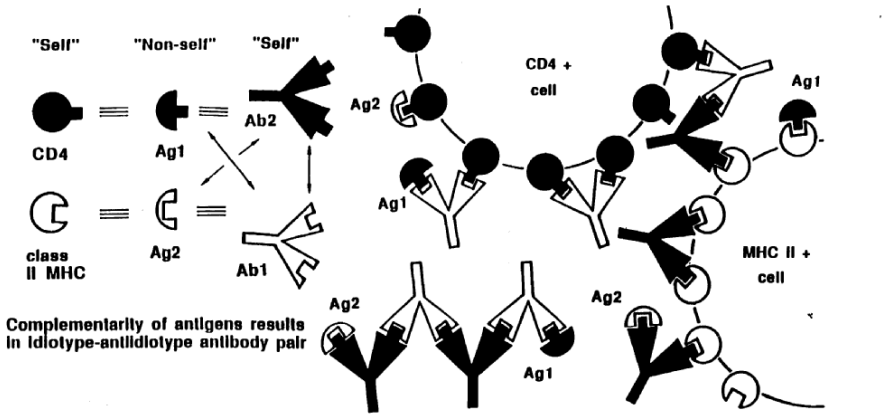
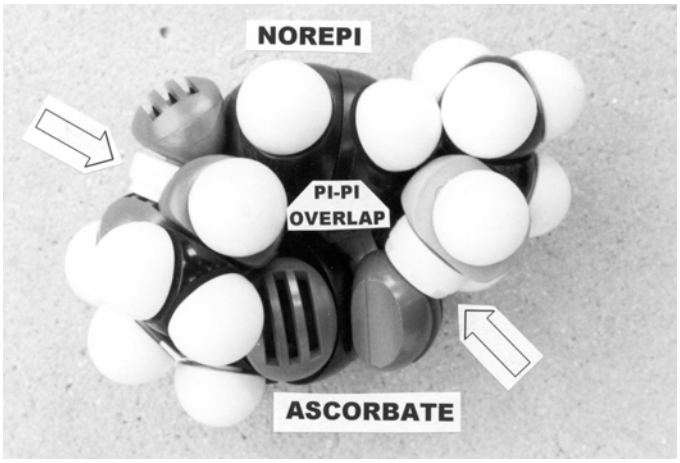
Our laboratory focuses on the many ways in which molecular complementarity has been employed by evolutionary processes in the development of metabolic control systems and in the immune system.




While some aspects of molecular complementarity are well-understood, including nucleic acid base pairing, receptor-ligand binding, enzyme-substrate interactions, and antibody recognition of antigens, many forms of molecular complementarity are still being discovered. These include our work on the complexation of small molecules such as ascorbate with adrenergic compounds; riboflavin with indoleamines (e.g., serotonin); catecholamines binding to opioid hormones; and hormone-hormone binding (e.g., insulin with glucagon). These small molecule interactions have been adapted to functional uses during the evolution of modern physiological regulatory systems. Ascorbate is stored wherever adrenergic compounds are synthesized (i.e., in the adrenals and in norepinephrine releasing neurons); riboflavin is a required cofactor in the synthesis of serotonin; catecholamine receptors co-localize with opiate receptors; etc. Moreover, we have discovered that receptor evolution itself has been directed by the physicochemical interactions of ligands for other small molecules: adrenergic receptors contain ascorbate binding sites that allosterically sensitize the receptor to adrenergic activation. Such sensitization by molecularly complementary compounds appears in many classes of receptors: glycine sensitizes the NMDA receptor to NMDA binding; benzodiazapines sensitize GABA receptors to GABA binding; etc. Thus, molecular complementarity between small molecules is reflected in functional complementarity.




We are systematically exploring the possibility that whenever a pair of molecules show functional complementarity, they are also physicochemically complementary; and conversely, whenever a pair of molecules bind to one another chemically, then they will display physiologically complementary functions. Demonstration of this hypothesis would obviously shed important light on the nature of the evolution of physiological systems in general. Notably, the hypothesis has also yielded a number of fundamental patents for improvements on asthma and blood pressure-related drugs.

In addition to our research on small molecule complementarity, we also explore the immunological implications, particularly with regards to the possible origins of autoimmune diseases. While it has long been known that antibodies are complements to their antigens, our lab is unique in exploring the consequences of challenging the immune system with a pair of molecularly complementary antigens. We have demonstrated, for example, that not only is insulin complementary to glucagon, but so are the antibodies induced by insulin and glucagon. Thus, insulin antibody specifically precipitates glucagon antibody. This fact also means that insulin antibody mimics glucagon itself, and that glucagon antibody mimics insulin. We are exploring the implications of this confusion of self-nonself for autoimmune complications in diabetes.

We have also discovered that many of the antigens associated with AIDS are molecular complements. In particular, antibodies against HIV specifically recognize and precipitate antibodies against other infectious agents associated with AIDS, including cytomegalovirus, hepatitis viruses B and C, and tuberculosis. We are exploring the implications of these antibody-antibody interactions for AIDS pathogenesis, the origins of lymphocytotoxic autoantibodies in AIDS, and various manifestations of autoimmunity.