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Cell migration and adhesion in early vertebrate brain development.

Summary:
The focus of my laboratory has been the study of migrating cells, both normal and abnormal, in the developing brain. This endeavor has utilized the chick embryo as the model system and recombinant retroviral vectors as a main tool to express or attenuate specific proteins. Investigating mechanisms of normal neuronal migration in the developing brain using retroviral vectors has led to related studies of programmed cell death, oligodendrocyte development, gene therapy, and the effects of the viral oncogene v-src. The transforming effects of v-src on migrating neurons have since been extended to the study of a particularly lethal form of abnormally migrating cell in the brain: gliomas.

In my laboratory we have uncovered basic mechanisms of normal vertebrate brain development, explored and established new in vivo models of human disease, and developed new *in vitro* technology that has been employed for the study of both.

Using the developing chick optic tectum (midbrain) as the model for vertebrate brain development, a variety of methods are used to investigate these processes. A main technology we use for this is retroviral gene transfer. Here, a recombinant retroviral vector carrying a marker gene and another cDNA (or its antisense copy) can be used *in vivo* to infect brain progenitor cells that line the ventricular cavity. The retroviral vector incorporates the recombinant DNA into the infected cell's genome and expresses it. Then, we can analyze how the expressed protein (or the antisense-attenuated endogenous protein) affects the cellular processes we are interested in.

Using this technique, we were the first to show that integrin extracellular matrix receptors were involved in brain development by using retroviral transduction in vivo of antisense sequences against β1 integrins. This caused infected neuroblasts to fail to migrate into superficial brain laminae, and then, to die. Similar experiments followed to show specifically that integrin heterodimers α6β1 and α8β1 were responsible for correct cell migration and survival, respectively. Replication-incompetent retroviral vectors are used when cell-autonomous effects are desired, and now we are using replication-competent vectors and *in ovo* electroporation to achieve widespread misexpression of several

proteins in the developing brain. We are investigating the roles of suspected integrin extracellular matrix substrates in migration and survival as well as the roles of other adhesion molecules (e.g. L1/NgCAM, contactin, the proto-oncogene c-src, and its viral counterpart oncogene v-src) in brain development.