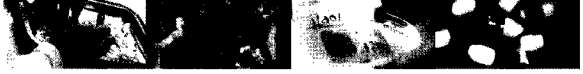

Keynote Lecture XV

Sonic Hedgehog Signaling: From Embryonic Development to Adult Disease

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Dr Rubin received his PhD in Neuroscience from The Rockefeller University and completed postdoctoral fellowships in Pharmacology from Harvard Medical School and in Neurobiology from Stanford University School of Medicine. He was then an Assistant and Associate Professor at Rockefeller University. Subsequently, he joined Athena Neurosciences (now Elan Pharmaceuticals) as head of their blood-brain barrier program, initiating work on an anti-lymphocyte trafficking antibody now known as Antegren. This antibody has been approved by the FDA as a therapeutic for multiple sclerosis. He then became Professor of Anatomy and Developmental Biology and Director of the Eisai Institute at University College London. This institute was sponsored by Eisai Co., a major Japanese pharmaceutical company, and focused on discovering novel therapeutic approaches to diseases of the nervous system. Finally, in 1998, he became Chief Scientific Officer of Ontogeny, Inc., now Curis, Inc. Work at Ontogeny and Curis has focused on the hedgehog pathway, a key regulator of embryonic development. They have been successful in identifying potent small molecule agonists and antagonists of this pathway. The agonists are potentially useful for treating neurodegenerative disease and have been partnered with Wyeth Pharmaceuticals for clinical development. The antagonists have been shown to be effective in an array of tumor models ranging from basal cell carcinoma and medulloblastoma to various other solid tumors. This project has been partnered with Genentech. The first hedgehog antagonist, a topical treatment for basal cell carcinoma will enter a Phase I study in 2005. Recently, they announced a new project supported by the Spinal Muscular Atrophy Foundation based on their ability to generate motor neurons from embryonic stem cells. Their goal is to identify a therapeutic for this devastating childhood disorder.

The signaling pathway regulated by ligands of the hedgehog (Hh) family is involved in the embryonic development of many tissue types. A great deal of work in the past 10 years has established that one of the ligands, sonic Hh, is particularly important for nervous system development. For example, proper numbers and types of spinal cord cells – motor neurons, in particular – are determined by exposure to the appropriate amount of secreted Sonic Hh. In addition, other important cell types in the central nervous system, including dopaminergic neurons, striatal GABAergic neurons, forebrain cholinergic neurons and oligodendrocytes, depend on having sufficient amounts of Sonic Hh present. Severe nervous system defects are a clear consequence of inadequate Hh signaling in species ranging from Drosophila to human.

It was, perhaps, not as obvious that the Hh pathway would also be involved in adult disease. The observation that Gorlin syndrome, associated with a highly increased frequency of basal cell carcinoma and predisposition to the development of other cancers including medulloblastoma, is due to a mutation in the Hh receptor patched (*PTCH*) stimulated a great deal of work directed at connecting various human cancers to aberrant Hh signaling. In addition, the Gorlin syndrome findings motivated us to identify potent small molecule antagonists of Hh signaling. All of this work has now culminated in the convincing demonstration that Hh inhibitors have real therapeutic potential in treating a variety of solid tumors. A phase I clinical study testing a topical Hh antagonist as a medicine for basal cell carcinoma is underway in collaboration with Genentech.

The knowledge that Hh signaling is also responsible for the generation of the very cells in the central nervous system that subsequently die in neurodegenerative disease (e.g., motor neurons in ALS and Spinal Muscular Atrophy and dopaminergic neurons in Parkinson's disease) prompted the discovery of small molecule agonists of the Hh pathway that are orally available and CNS permeant. These agonists have proven to be neuroprotective in a variety of disease models and to have the capacity for stimulating neurogenesis in the adult CNS. These agonists are now in preclinical development with Wyeth Pharmaceuticals.