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MOLECULAR STUDIES OF GENES IN MICE AND COMMON WORM MAY ACCELERATE RESEARCH ON BLOOD DISEASES, CANCERS

DALLAS – April 1, 2002 – Two studies led by a UT Southwestern Medical Center at Dallas scientist have revealed comparable genes that control what cells become in both mice and a common worm, findings that may lead to expediting research on human-blood diseases.

"We think we have found a way of efficiently studying how early blood-cell development is controlled and how gene defects in this process might lead to the development of blood diseases, including cancer," said Dr. Scott Cameron, an assistant professor of pediatrics and molecular biology and a pediatric oncologist who joined UT Southwestern in July.

His research, reported in the April 8 issue of the journal *Development,* found that the *pag-3* gene determines the fate of embryonic nerve cells in the microscopic worm C*aenorhabditis elegans*, a common soil nematode that became the first animal to have its genome sequenced.

"I showed that the gene in the worm, *C. elegans*, determines what the daughter cells will become after a cell division in the nervous system," Cameron said.

On the basis of what he and his colleagues learned from the worm, they collaborated in a subsequent study to knock out the counterpart mouse genes, which perform similar cell-determination functions but in the blood cells.

"In the gene-deprived mice, I found a defect in blood formation exactly consistent with what was predicted by the worm work," said Cameron, the principal investigator who collaborated with Dr. Stuart Orkin's lab at the Howard Hughes Medical Institute at Harvard Medical School and with Children's Hospital, both in Boston. The mice study was published first, in the February issue of *Genes & Development*.

His *pag-3* gene study found that a mutation resulted in a failure of the worm to develop neuron cells controlling forward and backward mobility. "Worms with the mutated *pag-3* do not move well," Cameron said.

The worm's uniform genetic patterns from egg to mature adult provide clues to uncovering the counterpart but more complex genetic patterns in mice, and mice patterns

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are closely akin to the still more complex human genetic mechanisms, he said.

Cameron's later mouse study revealed that when the *Gfi-1b* gene is muted in mice, their blood-stem cells fail to form red cells and platelets, causing mice embryos to die 11-12 days after fertilization. Related research has shown that knocking out the sister *Gfi-1* gene prevents development of certain white blood cells, resulting in the mice dying shortly after birth.

The blood-cell genetic defects in the mice were "precisely consistent with the defect identified in embryonic nerve cells in *C. elegans*. I can use forthcoming studies of cell development in the worm to tell me what experiments to do in the mouse," Cameron said.

"Different mutations in the *Gfi-1 gene* have been linked to some cancer tumors in mice."

Cameron hopes to find comparable links to cancer tumors in humans, though he cautions that gene numbers, roles, mutations and other variants contrast sharply between the mouse and human genomes and raise major challenges for human-disease research. "But I know that, overall, I'm in the right genetic neighborhood," he said.

Since the early 1960s, the study of microscopic *C. elegans* has yielded insights on mammalian genetics because, Cameron said, this worm is the only animal found to have known cell-division patterns that don't vary during maturation from fertilized larval egg to adult.

"One of the most abundant animal species on earth, the worm will eat your tomatoes," he noted, "but it has also become a powerful research tool."

His ongoing work, which could ultimately reveal a molecular pathway to reverse or modify blood-linked genetic defects, and the two recent studies began while he worked as a researcher and physician at the Dana Farber Cancer Institute of Harvard Medical School in Boston and the Massachusetts Institute of Technology in Cambridge.

Also contributing to the worm work were scientists at Howard Hughes research branches at Harvard and MIT, the Skirball Institute of New York University School of Medicine and the Louisiana State University Health Sciences Center at Shreveport. The *pag-3* study was supported by the National Institutes of Health and Howard Hughes Medical Institute at MIT.