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Mutant Mouse Mimics Human Bone Cancer

Howard Hughes Medical Institute (HHMI) researchers have developed a mouse model of osteosarcoma, the most common form of bone cancer. The new model will allow researchers to investigate the genetic underpinnings of the disease, as well as devise and test new drug therapies.

HHMI investigator Stuart H. Orkin of Children's Hospital and the Dana Farber Cancer Institute and his colleagues described the mouse model in an article published on June 16, 2008, in the journal *Genes & Development*. Andrew P. McMahon of Harvard University and HHMI investigator Frederick W. Alt at Children's Hospital, Boston were among the co-authors of the article.

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— **Stuart H. Orkin**

Osteosarcoma is a devastating cancer that usually affects adolescents and young adults, said Orkin. Even if surgery is done immediately to remove the bone tumor, the cancer spreads so quickly that a large fraction of patients die from metastatic cancer. The five-year survival rate is only about 60 percent, and the prognosis is poor once the cancer spreads.

Osteosarcoma results from the unregulated growth of osteoblasts, the cells that form the bone matrix. Bone tumors develop primarily near the ends of the femur, tibia or humerus, and are usually diagnosed during adolescence, when the long bones of the body undergo rapid growth.

There haven't been really any adequate animal models with which to study the mechanisms underlying osteosarcoma, particularly metastasis, or to

develop new therapeutic approaches, said Orkin. So having an animal model that genetically mimics the human cancer could have major benefits. New drug treatments are badly needed, he said, noting that physicians are treating osteosarcoma patients with the same drugs they were using 25 years ago.

In creating the mouse model, the researchers drew on studies by other researchers that implicated two genes, *p53* and *Rb*, in causing both sporadic and inherited forms of osteosarcoma.

In creating the genetically engineered mice, the researchers were confronted with a challenge - how to target the genetic alterations in *p53* and *Rb* only to osteoblasts. The researchers overcame that hurdle by basing their mouse model on a mouse strain developed by McMahon that permitted researchers to target expression of genes only to osteoblasts. Thus, the researchers were able to selectively shut down both *p53* and *Rb* expression only in the osteoblasts of adult mice.

They found that the mice developed osteosarcomas that closely resembled the human cancer, said Orkin. Furthermore, the same genes that are deregulated in humans who have osteosarcoma showed altered activity in the mice.

Perhaps the most interesting aspect of this model, in terms of its utility for studying the disease process, is that the mice show metastasis quite frequently, and to the same organs as in the human disease, said Orkin. This is relatively unusual for mouse models. In many such models, there is a large tumor, but not the kind of metastasis that approximates the human disease, he said.

The researchers also used an analytical technique called cytogenetic region enrichment analysis (CREA) to compare the chromosomal locations of affected genes in both the mice and in humans with osteosarcoma. Again, this analysis showed close resemblance between the mouse model and the human cancer. Orkin noted that CREA could also be used to validate whether other mouse tumor models faithfully represent the human disease.

Orkin and his colleagues plan to use the mouse model to detect whether particular patterns of gene activity influence the course of osteosarcoma, particularly metastasis. The model will prove valuable in identifying specific genes that control metastasis and that might be targets for new drugs to prevent spread of the cancer.

The mouse model also might provide a means to test an entirely new form of therapy for osteosarcoma, in which the osteoblasts—whose arrested development at an early stage drives the cancerous growth—are induced to mature, or differentiate, said Orkin. Differentiation could theoretically transform the cancerous osteoblasts back into normal cells, thereby halting the cancer, he said.