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Researchers Discover New Breast Cancer Gene

Scientists at Tularik Inc. (NASDAQ: TLRK) and Cold Spring Harbor Laboratory have discovered a new gene that is expressed at abnormally high levels in nearly 50% of the breast cancer specimens they examined, and is similarly overexpressed in a large proportion of lung cancers (35%).

The discovery of the gene, called KCNK9, is significant for several reasons:

- 1) KCNK9 reveals a previously unrecognized mechanism for oncogene action (namely, potassium channels).
- 2) KCNK9 is an attractive target for the development of novel cancer therapies.
- 3) The experimental overproduction of KCNK9 promotes tumor formation in controlled functional tests. This finding supports the notion that the overexpression of KCNK9 observed in breast and lung tumor biopsies plays a bona fide role in these cancers.

The study is also significant because it focussed on sporadic or non-heritable forms of breast cancer. Sporadic disease accounts for greater than 90% of all breast and other cancers, in contrast to heritable forms of cancer, which account for a relatively small percentage of the disease.

The study is published in the March 2003 issue of *Cancer Cell* and was funded in part by 1 in 9: The Long Island Breast Cancer Action Coalition. A copy of the study and illustrations are available on request.

The principle investigator is Scott Powers (Tularik Inc. Genomics Division and Adjunct Faculty member at CSHL). Other key contributors were the lead author David Mu of Tularik, and Michael Wigler, W. Richard McCombie, Scott Lowe, and their colleagues at CSHL. The scientists used a gene discovery method pioneered by Michael Wigler and his colleagues at Cold Spring Harbor Laboratory (called Representational Difference Analysis or RDA) to detect the differences between the DNA of normal cells and breast tumors—differences that might contribute to tumor formation. This analysis identified a small region (550 kb) of human chromosome 8 that was specifically amplified in the DNA of breast tumors.

The researchers used a variety of criteria to determine that the KCNK9 gene, one of only two genes in this region of chromosome 8, plays a role in cancer. Expression of the KCNK9 gene was increased at least five-fold and up to over 100-fold above normal levels in 28 out of 64 breast cancer specimens (44%), and in 35% of lung cancer specimens examined. In contrast, expression of the KCNK9 gene was not elevated in any of the normal tissue specimens examined.

To test whether increasing KCNK9 gene expression was sufficient to trigger cells to grow in a cancerous fashion, the scientists engineered cultured cells to produce increased levels of the KCNK9 protein. Then they examined whether such cells formed tumors when injected into mice more readily than when cells with normal levels of KCNK9 protein were injected into mice.

The results were clear: Tumors formed in 3 out of 5 mice within three months after they were injected with cells overexpressing KCNK9. In contrast, none of 5 mice injected with cells expressing normal levels of KCNK9 formed tumors.

This finding indicated that elevated KCNK9 levels are sufficient to trigger the cancerous growth of at least some cell types.

Dr. Wigler has previously used the RDA gene discovery method to identify a number of genes associated with sporadic breast cancer, including the tumor suppressors PTEN and DBC2. KCNK9 is the first oncogene to be unambiguously identified by using RDA, and may play a major role in the development of breast, lung, and other cancers.

Annual U.S. morbidity and mortality due to breast cancer are 200,000 and 40,000 people, respectively.

This press release contains "forward-looking" statements. For this purpose, any statements contained in this press release that are not statements of historical fact may be deemed to be forward-looking statements. Words such as "believes," "anticipates," "plans," "expects," "will," "intends" and similar expressions are intended to identify forward-looking statements. There are a number of important factors that could cause the results of Tularik to differ materially from those indicated by these forward-looking statements, including, among others, risks detailed from time to time in Tularik's SEC reports, including the report on Form 10-K for the year ended December 31, 2002. Tularik does not undertake any obligation to update forward-looking statements.