Scientists close in on method to fight deadly childhood cancer

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A multicenter team of researchers, including scientists from the University of Florida, has discovered a way to potentially block the growth of neuroblastoma, a type of cancer responsible for 15 percent of all cancer deaths in children.

Working with human cell lines and tissue samples, researchers describe in Thursday's (Oct. 16, 2008) online issue of *Nature* how they were able to short-circuit genetic processes that apparently contribute to neuroblastomas — tumors that arise from the developing nervous system in children and often appear in the abdomen, chest or neck.

Concentrating on a gene known as ALK, the scientists used a small-molecule inhibitor — a technique common to many drugs — to block abnormalities that apparently cause neuroblastomas.

Neuroblastomas are extremely rare, appearing in about 600 patients annually in the United States, according to the National Institutes of Health. About half of the patients with neuroblastoma are diagnosed before the age of 18 months. In 40 percent of cases, the cancer has spread to other parts of the body by the time doctors discover it.

Treatment usually involves surgery, chemotherapy and radiation, and transplantation for high-risk patients.

"We need to find a home run for these kids," said Wendy B. London, Ph.D., a research associate professor of epidemiology, biostatistics and health policy research at the UF College of Medicine and a member of the UF Shands Cancer Center. "A targeted therapy to treat patients with ALK mutations would be a real breakthrough."

Led by Dana-Farber Cancer Institute researchers Rani E. George, M.D., Ph.D., an assistant professor of pediatrics at Harvard Medical School, and A. Thomas Look, M.D., a professor of pediatrics at Harvard, the scientists analyzed the ALK gene in 94 tumors representative of general neuroblastomas and 30 neuroblastoma cell lines.

Scientists discovered that ALK abnormalities in a subset of neuroblastoma cells appear to interfere with the natural cell-death processes. Furthermore, they found some of the ALK mutations were sensitive to a tiny organic molecule known as TAE684, a discovery that may be useful in efforts to create drugs to staunch cancer growth.

In addition, researchers used gene-transfer techniques to initiate ALK-related cancer in rodent cells. These transduced neuroblastomas also appear vulnerable to the small molecule, known as an ALK inhibitor.

The tumor samples were obtained from the Children's Oncology Group Neuroblastoma Tumor Bank. COG is a NIH/National Cancer Institute cooperative research coalition that conducts pediatric cancer clinical and biological trials, including specimen collection and statistical analyses. The University of Florida is one of three sites of the COG Statistics and Data Center, where the study design, data collection and statistical analyses of the data take place.

The current findings dovetail with the recent discovery of the role of ALK mutations in both inherited and non-inherited versions of neuroblastoma published by researchers from The Children's Hospital of Philadelphia on Aug. 24 in Nature.

"This research group looked at neuroblastoma in a totally different and complementary way to ours and came up with similar results, validating the role of ALK mutations," said pediatric oncologist Yael P. Mosse, M.D., of The Children's Hospital of Philadelphia. "A unique aspect of their work is they proved in a model system that these mutations can indeed be cancer-causing."

With samples they had collected from families for the past 15 years, as well as additional data from the COG, Children's Hospital of Philadelphia scientists traced the genetic roots of many neuroblastomas to ALK mutations — findings that open the door to genetic screenings for the disease as well as possible therapies.

Ultimately, researchers hope drug treatments can be developed to disrupt the cancer cell-signaling process. They are designing a clinical trial that would test small molecules against the cancer-causing mutations in the gene.

"This is the epitome of translational research," said London, who is also the principal investigator of the COG Statistics and Data Center at UF. "We will use what we have learned about the sensitivity of ALK mutations to an ALK inhibitor and attempt to translate this knowledge to the development of targeted therapy for treatment of neuroblastoma patients in the clinic."

Source: University of Florida