

# Resistance of ER-positive breast cancer to tamoxifen therapy may be driven by APOBEC3B

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Responses to tamoxifen were significantly prolonged by reducing levels of the enzyme APOBEC3B in preclinical models of estrogen receptor-positive breast cancer and significantly shortened by increasing levels of APOBEC3B, suggesting that APOBEC3B drives resistance to tamoxifen, according to data presented at the 2015 San Antonio Breast Cancer Symposium, held Dec. 8-12.

In complementary clinical analyses, among patients with recurrent estrogen receptor-positive [breast cancer](#) treated with [tamoxifen](#), those who had high levels of APOBEC3B in their primary tumors had shorter durations of progression-free survival than those whose primary tumors had low APOBEC3B levels (medians of 7.5 versus 13.3 months).

"Several recent studies have linked elevated levels of the enzyme APOBEC3B in estrogen receptor-positive breast cancer with poor patient outcomes, but whether APOBEC3B actually drives the poor outcomes has not been determined," said Reuben Harris, PhD, investigator of the Howard Hughes Medical Institute, professor in the Department of Biochemistry, Molecular Biology, and Biophysics at the University of Minnesota, Twin Cities, and member of the Masonic Cancer Center. "Our preclinical studies using an established xenograft model of estrogen receptor-positive breast cancer show that APOBEC3B can drive [tamoxifen resistance](#).

"We know that APOBEC3B is not required for human life because a large proportion of people in Southeast Asia do not have APOBEC3B as a result of a natural genetic variation," Harris continued. "This, combined with the fact that it is an enzyme, makes APOBEC3B an attractive target for a therapeutic that could stop the development of resistance mutations and substantially extend the length of response to tamoxifen."

In preclinical studies, Harris and colleagues transplanted mice with a human estrogen receptor-positive breast cancer cell line called MCF-7L and then treated the mice with tamoxifen. Compared with mice receiving unmanipulated MCF-7L cells, mice receiving cells in which levels of APOBEC3B had been reduced by a technique called shRNA had significantly prolonged responses to tamoxifen and those receiving cells in which levels of APOBEC3B were increased by genetic manipulation developed tamoxifen resistance significantly more rapidly.

Harris noted that while the typical tamoxifen response of mice transplanted with unmanipulated MCF-7 cells was about 50 to 100 days, most of those transplanted with APOBEC3B-suppressed MCF-7 cells responded until the experiment was ended after a year; those transplanted with APOBEC3B-overexpressing cells developed rapid tamoxifen resistance with virtually no therapeutic response.

In collaboration with John Martens, PhD, an associate professor at Erasmus MC in Rotterdam, Netherlands, and Paul Span, PhD, an associate professor at Radboud University Medical Center in Nijmegen, Netherlands, Harris and colleagues also analyzed APOBEC3B levels in tumor samples from 285 patients with recurrent estrogen receptor-positive breast cancer. The tumor samples were obtained during surgery for primary breast cancer and all patients were treated with first-line tamoxifen therapy only after disease recurrence. Those patients whose tumors had high levels of APOBEC3B had disease progression

significantly sooner after starting tamoxifen therapy than those whose tumors had low levels of APOBEC3B: 7.5 months compared with 13.3 months.

Harris explained that APOBEC3B is an enzyme that causes [genetic mutations](#) and that this study suggests that by promoting genetic mutation it drives tamoxifen resistance. He also noted that this study indicates that APOBEC3B, as a dominant intracellular source of genetic mutation, could potentially be controlled to prevent cancer progression. Harris mentioned that we already know of external causes of cancer-driving genetic mutation that can be controlled—for example, ultraviolet radiation from the sun, which can be avoided by seeking shade or applying sunscreen, and cigarette smoke, which can be controlled by quitting—and APOBEC3B should be regarded as an analogous intracellular factor.

**More information:** Abstract: S4-07: Title: Tamoxifen resistance driven by the DNA cytosine deaminase APOBEC3B in recurrent estrogen receptor positive breast cancer

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