Breakthrough model for human cancer may improve development of cancer drugs

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AVEO Pharmaceuticals, Inc., a biopharmaceutical company leveraging breakthrough discoveries in cancer biology to discover, develop and commercialize targeted oncology therapies, today announced findings from its novel human-in-mouse (HIM) cancer model system, in which AVEO successfully created invasive human tumors from primary human breast tissue that develop over time in mice and mimic human tumor behaviors and response. The findings were published this week in the Early Edition of the *Proceedings of the National Academy of Sciences*.

More than 95 percent of oncology drugs entering the clinic fail, due in large part to the lack of predictive animal models in the preclinical development phases. AVEO scientists have developed a sophisticated cancer biology platform that provides models of human cancer more relevant than traditional mouse models known as xenografts. In the AVEO HIM model, normal human breast tissue is engineered to express oncogenes and is then introduced into mice where it forms human breast tissue in the mouse mammary microenvironment.

The tumors which then develop spontaneously acquire common and distinct mutations during tumor progression. This process results in human tumors in mice that reflect their human counterparts in that they differ slightly from one instance to another, exhibiting natural genetic variation akin to that seen in patients.

"Historically, the xenograft models created to analyze how human cancers behave have not been accurate predictors of human responses to

various therapeutic agents," said Robert A. Weinberg, Ph.D., member, Whitehead Institute and professor of biology, MIT. "In contrast, tumor development in the HIM model proceeds through defined histological stages of hyperplasia, from ductal carcinoma in situ (DCIS) to invasive carcinoma. Moreover, HIM tumors display characteristic responses to a targeted therapy known to be effective in humans, specifically Herceptin. This represents a big step forward in developing xenograft models that will accurately predict patient responses to agents that are in preclinical development. The HIM model is an exciting, experimentally tractable human in vivo system that holds great potential for advancing our basic understanding of cancer biology and for the discovery and testing of targeted therapies."

By employing a tissue recombinant system and a gene transduction system, researchers assessed the in vivo biological consequences of specific genetic alterations in the reconstituted breast tissue. Introduction of different combinations of oncogenes, such as HER2, KRAS, PI3 kinase and p53, into the tissue enabled the researchers to dissect the contribution of each gene to human tumor formation in the model.

The authors also demonstrated the utility of the HIM models for drug efficacy testing by treating the HER2 driven breast tumors with different HER2 antagonists. The resulting potent inhibition of HIM tumor growth correlates with what has been observed in the clinic.

"With the increasing knowledge of specific genetic alterations in breast cancer, there is now a significant opportunity to correlate activity of anticancer agents with specific genetic alterations in tumors," added Murray O. Robinson, Ph.D., senior vice president, oncology at AVEO. "Our proprietary models provide a defined genetic context in which to validate cancer gene candidates, determine their biological roles in various stages of cancer progression and test targeted therapies. We have been very encouraged by the similarity to human patients in response to

widely used breast cancer agents."

Source: Pure Communications Inc.