MedicalXpress

SU2C researcher identifies potential treatment option for melanoma

November 21 2013

Stand Up To Cancer (SU2C), the charitable initiative supporting ground-breaking research aimed at getting new cancer treatments to patients in an accelerated timeframe, announces that the Allan H. (Bud) and Sue Selig Stand Up To Cancer Melanoma Innovative Research Grant Recipient Roger S. Lo, M.D., Ph.D., associate professor in the Department of Medicine at the Jonsson Comprehensive Cancer Center of the University of California, Los Angeles (UCLA) has published two studies in *Cancer Discovery*, a journal of the American Association for Cancer Research which indicate that treatment using combinatory therapy may be effective in suppressing drug resistance in the treatment of melanoma.

Although most of the melanomas that harbor BRAF mutations respond dramatically to treatment with BRAF inhibitors, nearly all develop resistance to the drugs in less than a year, and previous studies showed that melanomas alter a cell signaling pathway called the MAPK pathway to become resistant. The new data published by Lo suggest a second pathway called the PI3K-PTEN-AKT pathway may also be altered and thus, a combinatorial therapy approach to target the two core survival pathways when treatment is initiated may suppress drug resistance.

"About 50 percent of melanomas are driven by mutations in the BRAF gene, and about 60-80 percent of these melanomas initially respond to BRAF inhibitors such as vemurafenib and dabrafenib, but most develop resistance within seven to eight months," said Dr. Lo. "Our goal is to study comprehensively how this cancer escapes from BRAF inhibitors,

so we can design new treatment approaches to overcome this resistance.

"It is very exciting to see work funded under a Stand Up To Cancer Innovative Research Grant (IRG) yield these important results," stated Sherry Lansing, co-founder & member of the SU2C Council of Founders and Advisors. "We created the IRG program to enable some of the best and brightest young researchers across disciplines to think out of the box and attempt to make major breakthroughs in their field with bold research projects." The SU2C IRG program is one of two initial funding models created by SU2C to focus on groundbreaking translational research aimed at getting new therapies to patients quickly. IRG grants support work that incorporates new ideas and new approaches to solve critical problems in cancer research. Dr. Lo's grant was one of the initial 13 IRG grants awarded in December 2009. Thirteen additional IRG grants were awarded in April 2011. To date, SU2C has funded $19.42 million for IRG research.

"There are several types of resistance, and one of these studies focused on early resistance, because most melanomas respond to BRAF inhibitors partially, leaving behind tumors subject to further evolutionary selection and development of late resistance," said Lo. "We found that suppressing the BRAF-regulated MAPK signaling quickly led to an increase in PI3K-AKT pathway signaling [causing early resistance] in many but not all melanomas. In those that do not display this early adaptive response, certain tumor subclones with the 'right' genetic variants in the PI3K-PTEN-AKT pathway would then have selective growth advantage during BRAF inhibitor therapy and eventually contribute to acquired [late] resistance," he explained.

Lo and colleagues studied melanoma tumors from patients collected before and early during treatment with BRAF inhibitors, and found that there was an increase in the amount of the activated form of a protein called AKT, early on after the start of treatment. They further confirmed

these findings using melanoma cells cultured in the laboratory. This increase in activated AKT was associated with various inhibitors that block MAPK signaling at different points along the pathway, such as BRAF and MEK inhibitors.

In an accompanying paper, Lo and colleagues analyzed 100 tumor samples from 44 patients whose melanomas developed late resistance to therapy with a BRAF inhibitor, either vemurafenib or dabrafenib. Samples represented tumors collected before therapy and after the development of late resistance when melanomas reacquired the ability to grow during therapy. By employing techniques including whole-exome sequencing and phylogenetic tree reconstruction, they found that 70 percent and 22 percent of the disease-progressive tumors had genetic alterations in the MAPK pathway and the PI3K-PTEN-AKT pathway, respectively. Both alterations were frequently found concurrently in the same tumor as well as in multiple tumors from the same patient.

These innovative projects are "high-risk" because they challenge existing research paradigms. IRG grant applicants are not required—as they would be by most conventional funding mechanisms—to have already conducted a portion of the research resulting in an established base of evidence. "If successful, the SU2C IRG projects have the potential for "high-reward" in terms of saving lives," explained William G. Nelson, M.D., Ph.D., a member of the SU2C Scientific Advisory Committee and director of the Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University in Baltimore, MD.

Dr. Lo's IRG grant is named in honor of Major League Baseball (MLB) Commissioner Allan H. (Bud) Selig and his wife Sue for melanoma research. MLB is Stand Up To Cancer's founding donor, and Commissioner Selig is a melanoma cancer survivor. The incidence of melanoma is rising, and the survival rate for those with advanced disease has been static at 15 percent. Nearly half of all patients with metastatic

melanoma have an alteration in a particular gene called BRAF, the target of Lo's investigations. "Lo's findings show that targeting both core pathways is a potential approach to achieve a much more meaningful remission or control of melanoma cancer and could significantly improve patient outcomes," concluded Dr. Nelson.

Provided by Stand Up To Cancer