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Anti-AXL biologic increases tumor sensitivity to radiation and check-point inhibitors

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New preclinical research published online today in *Nature Communications* suggests a potential role for Aravive-S6, a novel therapeutic candidate under development by Aravive Biologics, Inc., to increase tumor sensitivity to radiation therapy and check-point immuno-oncology agents.

Aravive-S6 is designed to selectively inhibit the AXL-signaling pathway which acts as a "survival switch" that scientists believe promotes tumor growth and metastasis, and resistance to common chemotherapeutic agents. The new research adds to evidence that AXL over-expression also results in tumor unresponsiveness to radiation and check-point inhibitors, and further shows that inhibiting AXL signaling elicits an anti-tumor immune response and sensitizes tumors to radiation and other anticancer therapies including PD-1 inhibitors and other immuno-oncology drugs.

The publication, entitled "Reprogramming the Immunologic Microenvironment through Radiation and Targeting AXL," was authored by Amato J. Giaccia, Ph.D., scientific founder and acting chief scientific officer of Aravive Biologics, and his research collaborators at Stanford University.

Dr. Giaccia commented, "Checkpoint inhibitors have demonstrated dramatic anti-tumor responses as single agents in about 10-30 percent of

patients, and there is increasing clinical evidence that these agents may achieve further anti-cancer synergies in combination with radiation therapy. Unfortunately, some tumors remain resistant to these approaches, and the aim of our research was to better understand the mechanisms underlying such resistance."

The researchers analyzed genetic, tumor micro-environmental, and immunologic factors in tumors derived from a transgenic model of breast cancer. They identified two tumors with similar growth characteristics but different responses to radiation therapy. Profiling the tumors revealed that the AXL receptor was over-expressed in the unresponsive tumors, and that knocking out AXL resulted in slower tumor growth, increased tumor sensitivity to radiation, and an anti-tumor CD8+ T-cell response that was improved with combination checkpoint immunotherapy.

"This research further increases our understanding of AXL as a key anticancer target, whose selective inhibition can overcome tumor resistance and increase the efficacy of a variety of anticancer agents, including radiation therapy and immuno-oncology approaches," said Dr. Giaccia. "Inhibiting AXL enhances MHC Class 1 expression, and recruits T-cells into the tumor by reversing the mesenchymal phenotype of the tumor to an epithelial phenotype. While the radiation and PD1/CTLA-resistant tumors were sensitive to AXL inhibition alone, the combination of anti-AXL and checkpoint inhibitors seems to work better in eliciting an anti-tumor response."

"Recently published preclinical research has shown Aravive-S6, our novel anti-AXL inhibitor, to exhibit potent preclinical activity against AML and advanced ovarian, pancreatic and breast tumors, both as a single agent and in synergy with cytotoxic drugs," said Ray Tabibiazar, M.D., President and Chief Executive Officer of Aravive Biologics. "This new research suggests that Aravive-S6 may also be a useful agent

in combination with checkpoint inhibitors such as PD1, PDL1 or CTLA4 inhibitors. We look forward to continuing our development of Aravive-S6, with a goal of filing an IND by the end of 2017."

More information: Reprogramming the Immunologic Microenvironment through Radiation and Targeting AXL, *Nature Communications*, DOI: 10.1038/ncomms13898

Provided by Aravive Biologics, Inc.