# New Research Suggests Role for Aravive Biologics' Anti-AXL Candidate for Increasing Tumor Sensitivity to Radiation and Check-point Inhibitors

-- *Nature Communications* publication describes mechanism by which AXL over-expression results in tumor unresponsiveness to radiation therapy and check-point inhibitors

-- Inhibiting AXL elicits anti-tumor immune response, sensitizes tumors to radiation and anticancer therapies including immuno-oncology approaches

-- Aravive-S6 acts as "decoy receptor," binding Gas-6 to prevent AXL activation

**HOUSTON, TX (December 23, 2016):** 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 PD1 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.”

**About Aravive-S6**

Aravive-S6 is a novel therapeutic candidate that in preclinical research has shown strong, highly selective preclinical activity against multiple advanced forms of cancer as both a single agent and in synergy with other anticancer drugs. A novel fusion protein, Aravive-S6 acts as a decoy that binds Gas-6 with high affinity to prevent its triggering of the AXL signaling pathway, a key “survival switch” that scientists believe promotes tumor growth and metastasis, and resistance to other anticancer agents. AXL-inhibition has been attributed with causing DNA replication stress and perturbing DNA replication and repair, as well as triggering immunological activity that leads to enhanced tumor cell death. This mechanism suggests that the combination of Aravive-S6 with other anticancer agents, including radiation therapy, immuno-oncology agents, and drugs that affect DNA replication and repair, including PARP inhibitors, may offer an exciting new avenue for improving cancer therapy.

**About Aravive Biologics, Inc.**

Aravive Biologics is a privately held, late preclinical stage biopharmaceutical company developing novel, highly selective cancer therapies that treat serious malignancies while sparing normal healthy cells. The company’s lead program is focused on the GAS6/AXL pathway, where activation appears to play a critical role in multiple types of cancer malignancies by promoting tumor metastasis and cell survival. Aravive Biologics has generated strong preclinical data for its lead drug candidate, Aravive-S6, in both acute myeloid leukemia (AML) and solid tumors including ovarian, pancreatic, and breast cancers. The company is based in Houston, Texas, and receives support from the Cancer Prevention & Research Institute of Texas (CPRIT). For more information, please visit our website at http://www.aravive.com.

**Forward-Looking Statement**

This press release contains forward-looking statements. Forward-looking statements contained in this press release include, without limitation, statements regarding the timing of the IND filing, the expected role of the Aravive-S6 Fc-fusion protein in blocking the activation of the GAS6-AXL signaling pathway, the timing of commencement of clinical studies, and intended use of Aravive Biologics' complementary diagnostic tool to identify patients with cancers exhibiting elevated GAS6 levels. Words such as "may," "believe," "will," "expect," "plan," "anticipate," "estimate," "intend" and similar expressions (as well as other words or expressions referencing future events, conditions or circumstances) are intended to identify forward-looking statements. These forward-looking statements are not guarantees of future performance and involve a number of unknown risks, assumptions, uncertainties and factors that are beyond Aravive Biologics' control including the ability of Aravive-S6 to serve as a decoy that prevents the binding of GAS6 to the AXL receptor on tumor cells and the ability of Aravive Biologics' companion diagnostic tool to identify patients with cancers exhibiting elevated GAS6 levels. All forward-looking statements are based on Aravive Biologics' expectations and assumptions as of the date of this press release. Actual results may differ materially from these forward-looking statements. Except as required by law, Aravive Biologics expressly disclaims any responsibility to update any forward-looking statement contained herein, whether as a result of new information, future events or otherwise.

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