New Research Validates both Single Agent and Synergistic Anticancer Activity for Aravive Biologics' Anti-AXL Candidate in Multiple Tumor Types

- *Journal of Cancer Investigation* article shows that in preclinical studies Aravive-S6 achieves anti-tumor effects through highly selective, potent inhibition of AXL-signaling, resulting in DNA replication stress
- Preclinical studies show lack of toxicity and superior anticancer activity for Aravive-S6 against AML and advanced ovarian, pancreatic and breast tumors, both as a single agent and in synergy with cytotoxic drugs, compared to current small molecule AXL-inhibitors
- Mechanism of action suggests broad utility of combining Aravive-S6 with other anticancer drugs that perturb DNA replication and repair, including PARP inhibitors

Houston, TX (November 29, 2016): Aravive-S6, a novel therapeutic candidate under development by Aravive Biologics, Inc. shows strong, highly selective preclinical activity against multiple advanced forms of cancer as both a single agent and in synergy with other chemotherapeutic drugs, according to new research published today in the *Journal of Cancer Investigation*. Aravive-S6 is attributed with selectively inhibiting the AXL-signaling pathway which acts as a "survival switch" that scientists believe promotes tumor growth and metastasis, and resistance to common chemotherapeutic agents. In addition, AXL-inhibition has been attributed with causing DNA replication stress and perturbs DNA replication and repair, leading to enhanced tumor cell death. This mechanism of action suggests that the combination of Aravive-S6 with other agents that affect DNA replication and repair, including PARP inhibitors, may offer an exciting new avenue for improving cancer therapy.

The co-senior author of the *JCI* research publication, entitled "Augmenting the efficacy of chemotherapies by inhibiting the Gas6/AXL pathway," is Amato J. Giaccia, Ph.D., scientific founder and acting chief scientific officer of Aravive Biologics, which holds an exclusive license from Stanford University to Aravive-S6 and the research findings described in *JCI* paper. He collaborated on the work with researchers at Stanford.

"This research adds to our understanding of AXL as an anticancer target in two critical ways," said Dr. Giaccia. "First, we provide support that Aravive-S6 is a very selective and potent biologic that shows evidence of superiority over the current pipeline of anti-AXL compounds. More importantly, by demonstrating that inhibiting AXL adds to the replicative stress faced by cancer cells, we suggest a way to improve the efficacy and therapeutic index of both standard cytotoxic chemotherapies and other agents that perturb DNA replication and repair, such as PARP inhibitors."

Targeting AXL Signaling to Block Disease Progression

As understanding of the molecular basis of cancer has improved, researchers have identified a number of signaling pathways responsible for driving disease progression. In many cases, however, the genetic instability and high mutation rates that occur in cancer, coupled with the redundancy often built into biological systems, have limited the usefulness of therapies directed against such targets. The AXL receptor, in contrast, appears not to become mutated in cancer, and in fact becomes elevated as tumors evolve and experience increased DNA damage. AXL signaling, triggered by the binding of Gas6 to AXL, drives tumor progression and metastasis, as well as the ability of tumors to become resistant to many chemotherapeutic drugs. In several tumors types, including acute myeloid leukemia (AML) and advanced forms of ovarian, pancreatic and breast cancers, targeting AXL has been shown to have beneficial anticancer effects. However, drug candidates targeting AXL -- mostly small molecule kinase inhibitors (TKIs) -- have shown either limited efficacy and/or considerable toxicity in studies to date.

In the published studies, the researchers tested a novel fusion protein, Aravive-S6, which has been designed as a "decoy" receptor to strongly bind Gas6 with high levels (sub-picomolar) of affinity, and thus prevent the triggering of the AXL pathway. The researchers showed the ability of the decoy alone to induce cell killing in AML cells and significantly inhibit disease progression in aggressive models of ovarian, pancreatic and breast cancer. In these preclinical research studies, when the authors directly compared the decoy molecule to the most advanced anti-AXL TKIs in the clinic, Aravive-S6 achieved superior anti-tumor efficacy while displaying no signs of potential toxicity. Moreover when Aravive-S6 was combined with standard chemotherapeutic drugs, even greater anticancer efficacy was seen in multiple tumor models. Moreover, in a preclinical model of human advanced ovarian cancer, the treatment combination is attributed with reducing tumor burden by more than 99%, and three out of 10 treated animals had no evidence of disease after treatment.

In a result that was surprising to the investigators, they found evidence that AXL signaling provided cyto-protection for tumor cells and the loss of AXL signaling led to replicative stress and the activation of the DNA damage response. "DNA damaging agents have long been used to take advantage of cancer's hyperproliferative state, and we have shown that modulation of the DNA damage response by inhibiting AXL can increase the therapeutic effects of those drugs both in laboratory and animal studies," said Dr. Giaccia. "Our results suggest that anti-AXL therapies such as Aravive-S6 can be broadly used to heighten the effects of cytotoxic and other agents across a broad spectrum of cancers. This finding is particularly exciting for the strategy of combining Aravive-S6 with PARP inhibitors, which also act by disrupting DNA replication."

"We are extremely excited about these findings, which support our ongoing development efforts with Aravive-S6 in AML and certain aggressive solid tumors where AXL is shown to play a key role in drug resistance and cancer survival," said Ray Tabibiazar, M.D., President and Chief Executive Officer of Aravive Biologics. "We continue to work towards entering the clinic with a goal of filing IND by end of 2017."

About Aravive Biologics, Inc.

Aravive Biologics is a privately held, late pre-clinical 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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