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HEATING UP COLD TUMORS

Dual-action, dual-indication decoy fights tumors, viruses

By Anette Breindl, Senior Science Editor

Inhibiting the Axl kinase could have applications in both antitumor and antiviral therapy, separate papers published over the past few weeks have reported. In the Jan. 10, 2017, issue of *Cell Reports*, a team from the French INSERM Institute showed that Axl receptor activity both enabled Zika virus entry into cells and modulated innate immune responses.

Separate publications in the Dec. 23, 2016, issue of *Nature Communications* and the Nov. 28, 2016, issue of the *Journal of Clinical Investigation* reported that targeting Axl could sensitize tumors to radiation, checkpoint inhibitors and chemotherapy.

Cancer cells are "very smart – when you make a move, they make a move," Ray Tabibiazar told *BioWorld Today*. "They have these amazing adaptive responses," ultimately developing resistance to many treatments.

Tabibiazar argued that those adaptive abilities are ultimately the problem in treating many tumors. "Five to six years ago, it was all about the genetic drivers," he said. But "it's not the genetic driver that makes the tumor survive, it's the adaptive response."

Tabibiazar is the CEO of Aravive Biologics Inc., which is developing the Axl decoy receptor Aravive-S6.

Aravive's scientific co-founder, Amato Giaccia, is the senior author of both the *JCI* and the *Nature Communications* paper. Aravive-S6 itself was used in the *Cell Reports* and *JCI* papers, while the authors of the *Nature Communications* paper used Axl knockouts in their work.

Axl and its ligand, Gas6, were first found to be important in leukemia, but Aravive – which changed its name from Ruga Corp., and its location from South San Francisco to Houston, in November 2016 – has studied Aravive-S6 in a number of indications, including triple-negative breast cancer (TNBC), resistant pancreatic, renal, ovarian and EGFR-resistant lung cancers.

Axl activity affects tumors in multiple ways. Axl and Gas6 are "the primary drivers" of epithelial to mesenchymal transition (EMT), which increases the ability of tumor cells to move around.

Axl also interacts with the DNA damage response, and Tabibiazar expects knowledge of that mechanism will be helpful in designing clinical trials. "We know exactly which patients our drug will work well with," he said.

In tumor-immune system interactions, the effects of Axl/Gas6 are twofold. High levels of Axl's interaction partner Gas6 recruit macrophages, which protect the tumor. And high levels of Axl itself lead to lower levels of antigen-presenting major histocompatibility complex (MHC) molecules, which makes tumors less visible to the immune system. Tabibiazar described blocking Axl as "taking the tumor's invisibility cloak away."

The company plans to file an IND in an oncology indication for Aravive-S6 by the end of 2017. "For the clinic, in solid tumors, the combination with checkpoint inhibitors makes a lot of sense," Tabibiazar said. "Checkpoint inhibitors do not work in a cold tumor, and Axl inhibition may turn cold tumors" – i.e., those that are not infiltrated by immune cells – "hot."

As far as the decoy's antiviral potential goes, "if we move it forward, it will be through a partnership," he said.

The antiviral effects of blocking Axl are broadly analogous to its antitumor effects in that although Aravive-S6 acts partly by blocking viral entry, most of its effect is on the host response rather than the virus itself.

That focus on the host in combination with the fact that Gas6 is used by several viruses that are ongoing or intermittent public health threats with little in the way of treatments – Dengue, Zika and Ebola, and Marburg viruses – could translate into broad-spectrum potential for Aravive-S6.

Developing broad-spectrum antivirals by focusing on the host immune response is getting attention in other quarters, too, as evidenced most recently by the founding of Vir Biotechnology Inc. with $150 million. (See *BioWorld Today*, Jan. 9, 2017.)

In Tabibiazar's opinion, such focus on the host immune system is overdue. "Every two or three years, there's one of these outbreaks. And we're always trying to chase the virus . . . and we can't be chasing after every one of them," he said. "We have to come to a little bit broader view."