

## Product Development

# Spinning more KSP inhibitors

**By Aaron Bouchie  
Senior Writer**

Disrupting mitosis is a well-validated method to treat cancer, but current drugs that disrupt the process, such as taxanes and vinca alkaloids, also target neural cells and cause peripheral neuropathy. A host of biotech and pharma companies are taking new approaches to mitosis disruption, with inhibitors of kinesin spindle protein (KSP) one of the most prominent.

Array BioPharma Inc. last week put its first KSP inhibitor into a Phase I trial for solid cancers, joining Cytokinetics Inc. and Merck & Co. Inc. in the clinic with compounds that target this mitotic protein.

The Phase I study of ARRY-520 will be in late-stage cancer patients with solid tumors who have already failed three or four therapies. ARRY (Boulder, Colo.) also plans to test the compound in hematologic cancers.

CYTK (South San Francisco, Calif.) was the first company to move a KSP inhibitor into the clinic: ispinesib, a quinazolinone it discovered and then partnered with GlaxoSmithKline plc (LSE:GSK; GSK, London, U.K.). Ispinesib has entered nine Phase II trials and seven Phase I/Ib studies. Four of the Phase I/Ib trials have finished. Final data from three of the Phase II trials have been released, none of which met primary endpoints.

The partners also have started two Phase I studies of SB-743921, a second-generation KSP inhibitor they discovered together.

Kevin Koch, president and CSO of ARRY, would not disclose details of ARRY-520's chemical composition. But he said it is a member of a different compound class with a lower molecular

weight than quinazolinones, is more soluble and tends to be more potent based on internal tests.

"ARRY-520 shows more preclinical efficacy and a more durable response in tumors than ispinesib," he said. "We can give a higher dose and get a longer duration of response, both of which we view as positives. Basically, ARRY-520 hits the target harder in the tumor than ispinesib does."

ARRY-520 works against taxane-resistant cell lines, but Koch has not yet compared the compound against newer anti-mitotics, such as epothilones being developed by Bristol-Myers Squibb Co. (BMJ, New York, N.Y.) and Novartis AG (NVS; SWX:NOVN, Basel, Switzerland), among others.

CYTK President Robert Blum said both SB-743921 and ARRY-520 are about five times more potent than ispinesib, but noted that a compound's potency is only one of several relevant factors. "Specificity, how the drug distributes to the tissue, pharmacokinetics, potency, they all come together for activity," he said.

Blum noted CYTK's second-generation compounds are different in pharmacokinetic profile and how they distribute to the tissue. "These might have activity in hematologic cancers," he said. "Ispinesib could eventually be for solid tumors and SB-743921 for hematologic cancers."

Blum added that CYTK will move forward with ispinesib in breast cancer because the partners saw clinical activity with the compound alone and in combination with capecitabine. He said they also saw activity in platinum-sensitive lung cancer, but have not yet decided whether to pursue that indication.

This year, CYTK and GSK also plan to start a Phase I study



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of GSK-295, which targets centromere-associated protein-E (CENP-E), another mitotic kinesin. According to Blum, CENP-E acts when chromosomes are lined up in metaphase, and its inhibition induces cell cycle arrest and cell suicide. KSP acts earlier in mitosis when the bipolar scaffold is being established, and its inhibition induces apoptosis.

“It is unclear which target might be better suited for which cancers,” Blum said. “The proof will be in clinical studies.”

Meanwhile, MRK (Whitehouse Station, N.J.) has completed a Phase I trial of its MK-0731 KSP inhibitor. Fourteen patients received a 24-hour infusion of the compound, and no objective responses were observed.

MRK would not comment, but Blum said that the data suggest MK-0731 might have administration limitations. “Its compound was dosed for 24 hours and did not shrink tumors,” he said. “They might have figured out how to dose it better since then, but cancer patients won’t want to sit for 24 hours when a one-hour dose is typical.”

Other companies with inhibitors of KSP (also known as Eg5) include Eli Lilly and Co. (LLY, Indianapolis, Ind.), which licensed a preclinical KSP inhibitor from Kyowa Hakko Kogyo Ltd. (Tokyo:4151, Tokyo, Japan) last year.