

PRIMATES TRANSLATE, PRV POSSIBLE

Ricin to the challenge: Bid with vaccine excites Street; Soligenix is 'only game' now

By Randy Osborne, Staff Writer

Having results in primates with its ricin toxin vaccine Rivax is "almost like you've got phase II data," Soligenix Inc.'s chief scientific officer Oreola Donini told *BioWorld Today*, which is probably why shares of the Princeton, N.J.-based company (NASDAQ: SNGX) skyrocketed 43.6 percent, or \$1.12, to close Wednesday at \$3.69.

"We're pretty much the world leaders and the only game in town," Donini said, although the U.S. Department of Defense "does have a ricin vaccine they call Rvec. It's a little bit earlier in the development cycle, and I think has been subject to funding uncertainty in the government framework. They haven't done much in the last few years."

Unlike Soligenix, which has done plenty. Investors hailed word that results from the Rivax development program will be presented at the annual Conference on Vaccine Research in Bethesda, Md., next week. The vaccine, formulated with Thermovax, Soligenix's heat stabilization technology, has turned up significantly enhanced thermostability and 100 percent protection in preclinical ricin models in which aerosol was tried, the company said.

Lethal, plant-derived ricin is of special concern as a biological weapon. "It's relatively easy to produce," Donini said. "You can grow castor beans and isolate it from the mash [in] a fairly straightforward procedure." A tiny amount of ricin "can poison by a number of routes, but it's most potent when inhaled. You can also ingest it, and it can have side effects that way, albeit you need to ingest more." Although anthrax grabs headlines, ricin is "easier to make and easier to deliver, especially in a small, enclosed space" by way of aerosol, she said, calling the substance "quite scary, from that perspective."

Although Wall Street seemed to have gotten the message loud and clear, Donini said that approval sought under the animal rule with the FDA can be "tricky for people to understand." Definitive proof that the vaccine works "is going to be a good laboratory practice efficacy study in primates, which is what we're preparing for," she said. "We already do have significant safety data from phase I studies in humans, which is the only human study you

can do. Obviously, you're not going to poison humans with ricin." Soligenix could qualify for a priority review voucher (PRV) with Rivax. "Certainly, we appear to meet all of the criteria listed in the legislation," she said, referring to the 21st Century Cures Act. "Obviously, nothing is done until it's done, but [the PRV] does appear very feasible." In biodefense, a PRV may be awarded upon the product's approval as a medical countermeasure when the active ingredient(s) have not been otherwise cleared for use in any context. PRVs are transferable and can be sold, with sales in recent years ranging between \$125 million to \$350 million. (See *BioWorld Today*, Aug. 20, 2015, and Feb. 22, 2017.)

The animal rule is "a less well-trodden path with the FDA, although clearly [Rivax] fits very neatly into that category," Donini said. "At the moment, we have a National Institute of Allergy and Infectious Diseases [NIAID] contract where we're pursuing good manufacturing practices manufacturing, with the aim of conducting [the] key studies." Following the current timelines, approval could happen "as early as a couple of years" from today, she said.

Ricin toxin has two components, the A chain and B chain. "We took the A chain, made some mutations to it so that it's not toxic anymore by itself, and then used that as the antigen for the vaccine," Donini said. "So it's a subunit vaccine, and those always have the advantage of being a bit safer." The product uses aluminum salts, or alum, as the adjuvant, and Thermovax "works specifically even in the presence of alum, which has traditionally been a challenge. We've been able to create a very stable and potent vaccine as a result" of applying it to the vaccine, she said.

Biodefense initiatives by the government are "encouraging industry to move into the space," and contracts such as those with Biomedical Advanced Research and Development Authority have "tried to drive [research] in this direction. I can't really say why no one else is in the ricin toxin vaccine

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space, although at this point our candidate is fairly advanced.”

Once the vaccine, which is designated an orphan drug, is cleared by regulators, distribution “could work a couple of different ways,” she said. Rivax is “relevant for the war fighter, but I think it’s also very relevant for first responders, if you think about having them protected in a more pre-emptive setting. That’s something that will be worked out through discussions with the government” in the U.S. and potentially those in other countries.

A phase Ia trial with a formulation of Rivax that did not contain an adjuvant turned up dose-dependent seroconversion as well as lack of toxicity when given intramuscularly to human volunteers. The adjuvant-free form induced toxin-neutralizing antibodies that lasted up to 127 days after the third vaccination in several people, Soligenix said. To increase the longevity and strength, Rivax was next made with the alum adjuvant for a phase Ib trial that proved the vaccine safe and well tolerated, inducing greater ricin-neutralizing antibody levels in humans than the adjuvant-free version.

‘ASSASSIN’S TOOL’ WORTHY OF STOCKPILE: EXPERT

In early February, the ricin terror threat reared its head when a Georgia man, said to belong to a white supremacist group, was charged with possession of the substance after he sought medical treatment for exposure to it. Another incident last November highlighted the dangers. The staff at the Federal Emergency Management Agency (FEMA) Center for Domestic Preparedness, while making a purchase of ricin A-chain for training, recognized “an ongoing discrepancy in the documentation related to the type of ricin” being provided, the agency said. The vendor had been supplying FEMA since 2011. “Upon learning that a more toxic version of ricin had been received, and out of an abundance of caution,” all chemical and biological operations were halted, FEMA said, and “any training affected or postponed [would] be rescheduled pending the completion of our assessment and the implementation of any recommendations for improved processes at the facility, if appropriate.”

Ricin has been investigated for beneficial effects as well, Donini noted, citing work done by molecular immunologist Ellen Vitetta, director of the Cancer Immunology Center at the University of Texas Southwestern Medical Center (UTSW) in Dallas, and her team. “They were looking at whether they could direct ricin specifically to tumors and use it to poison the tumors,” she said,

specifically by using an antibody that would deliver ricin to the cancer’s front door. The vaccine Rivax originated at UTSW, and its development has been sponsored by way of a series of grants totaling about \$25 million so far from NIAID to Vitetta’s researchers. The FDA put in money for the effort, too. (See *BioWorld Today*, March 13, 2002.)

Amesh Adalja, senior associate at the Johns Hopkins University Center for Health Security with a special interest in biothreat agents, told *BioWorld Today* that labs have “been working on these vaccines for some years now,” and the uphill climb is finally yielding results.

“This is a problem we’ve seen with many different biothreat agents: that we don’t really have many countermeasures being made because there isn’t really a market other than the one that the government creates,” he said. Developers have “had problems with stability, and that’s taken some time to sort out. They had to use an adjuvant to put this together so the immune system would be stimulated enough. Also, it’s unclear what is the correlate for protection. Is the antibody that’s formed by the vaccine protective against this poison?”

Further causing a lack of interest in ricin is the fact that it’s classed by NIAID as a category B toxin, less critical than category A, which includes the likes of anthrax, botulism, plague, smallpox, tularemia and the viral hemorrhagic fevers. “We’ve had an anthrax vaccine for a long time and we have an Ebola vaccine, but these were things that weren’t considered to be high priorities by the pharmaceutical industry because they were so rare and not really commercially viable outside of government funding,” Adalja said. Although “there hasn’t been a big effort [in ricin], I do think that the progress that has been made with the two vaccines has been substantial and it’s well worth having a ricin vaccine in the stockpile.” Ricin is “more of an assassin’s tool” than a weapon of mass destruction, he said. “When you’ve seen it used before, it’s been used in one-off types of things.”

In 1978, a Bulgarian Cold War dissident named Georgi Markov was jabbed in the leg with an umbrella’s tip while he waited for a bus. He died four days later. In 2013, an Elvis impersonator was charged with sending ricin-laced letters to President Obama. Despite their rarity so far, ricin attacks represent “something that is important to be prepared for” on a wider scale, Adalja said.