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Cequent Releases Primate Safety, Efficacy Data for Oral FAP Therapy

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Newsletter: RNAi News

Cequent Pharmaceuticals this week unveiled non-human primate data demonstrating the safety and gene-silencing ability of its lead drug candidate, a treatment for familial adenomatous polyposis dubbed CEQ501, in what the company is calling the first proof of activity of an oral RNAi drug.

With these data in hand, Cequent remains on track to begin a phase I study of CEQ501 before the end of the year, a company official confirmed. At the same time, Cequent's efforts in inflammatory bowel disease are proceeding apace as the company evaluates a number of potential targets, including ones not covered under an option agreement with Novartis, the official said.

Like all of Cequent's drug candidates, CEQ501 is based on the company's so-called transkingdom RNAi technology, which involves using attenuated *Escherichia coli* to transcribe therapeutic shRNAs.

According to the company, the bacteria express the protein invasion on their surface, which allows them to enter a host cell. They also express listeriolysin, which permits the shRNA payload to escape after bacterial entry.

In 2006, Cequent researchers reported that tkRNAi bacteria expressing shRNAs against the oncogene beta-catenin could inhibit target expression in the intestinal epithelium of a mouse model. Intravenous administration of the transkingdom RNAi drug to mice carrying colon cancer xenograft tumors, meanwhile, resulted in a significant drop in beta-catenin expression and reduced cell proliferation. In light of these findings, the company set its sights on FAP as an initial indication that could showcase the technology's potential.

FAP is an inherited, colorectal cancer syndrome characterized by the growth of colorectal polyps. Though the polyps are initially benign, they become malignant in nearly all cases in the absence of colectomy, according to the company. But by targeting beta-catenin, Cequent hopes that CEQ501 will prevent new polyp formation and possibly slow the progression to malignancy of existing ones.

Without treatment, patients with this orphan disease "have a 100 percent risk of colon cancer," Johannes Fruehauf, Cequent's vice president of research, told *RNAi News* last week. "The usual medical management is to remove the colon if the polyp number becomes too great. Our hope is that with this treatment, we can … help [patients] keep their colons longer by preventing the formation of new polyps, or at least slowing" the polyp-formation process.

Buttressing Fruehauf's comments are new monkey toxicology data, presented in a poster at the Keystone Symposia's Therapeutic Modulation of RNA Using Oligonucleotides conference this week, indicating that orally administered CEQ501 inhibits beta-catenin expression in target tissue and does not cause any adverse events.

In the study, 18 monkeys were divided evenly into three groups to receive CEQ501 at dosages of 10^9, 10^{11}, or 10^{12} cfu/dose via nasogastric tubes once a day for 28 days. Four control animals received no treatment.

Four monkeys from each treatment group were then sacrificed at either 2 hours or 24 hours following the last dose, Fruehauf explained. The remaining animals were allowed to recover for 21 days without treatment and then were sacrificed.

All three dose levels were well-tolerated with no treatment-associated adverse events observed, he noted. Tissue samples from the large and small intestine showed that drug treatment was effective in roughly 84 percent of the animals, with around 60 percent inhibition of beta-catenin expression levels in the intestinal mucosa compared to controls.

Additionally, pharmacokinetic analysis confirmed the presence of the engineered shRNA in the mucosa two hours after dosing, "proving successful delivery of the active hairpin RNA component by the bacterial system," according to Cequent's poster.

In the animals allowed to recover, restitution of gene-expression levels were observed by day 21, Fruehauf noted. "We don't have any data from any shorter time points … and believe that the recovery could have been observed even earlier … [but] we know at 21 days the gene-expression levels were back to normal," he added.

The investigators did not examine the levels of beta-catenin expression in other organs in the gastrointestinal tract, Fruehauf said, but they did examine the animals' serum throughout the study for cytokine induction.

"If any bacteria got out of the gut, there would be, of course, cytokine responses," he said. "We don't see any of that."

Currently, Cequent is finishing up a handful of toxicology studies requested by the US Food and Drug Administration during a pre-investigational new drug application meeting with the company last year (see *RNAi News*, 5/8/2008). Once this work is finished, Cequent plans to file an IND on CEQ501 to begin a phase I trial of the drug late in the year, although the design of that study has changed slightly from what the company was previously anticipating.

Cequent had initially planned to enroll 30 FAP patients in a dose-escalating trial that included extended periods between the times when patients would receive higher doses of the drug in order to make sure there were no adverse events at the lower doses.

But because of the "very positive experience with the monkey toxicology study, where we saw no signs of toxicity in any of the dosing groups," Cequent has re-designed the trial to include a more rapid dosing schedule, Fruehauf told *RNAi News*. "This will also allow us to complete the trial in a shorter time than originally scheduled and then, hopefully, move on to a larger phase II study."

Under the new phase I study protocols, 12 FAP patients will be divided into four dosing groups. The first patient in the lowest-dose cohort will be treated for one week, after which two others will begin treatment.

"The next dosing level will be started by enrolling the first patient at the next level if all patients in the lower level have tolerated the lower dose well for at least one complete week," Fruehauf wrote in his e-mail.

As with all phase I studies, the primary endpoint is safety. But Fruehauf said that intestinal biopsies will be taken in order to evaluate mucosal beta-catenin levels, "which can be used as a sort of efficacy

readout."

Assuming a positive outcome to the trial, a phase II study is expected to begin in 2010, according to Cequent.

IBD

In parallel with FAP, Cequent continues to advance its IBD program, which includes both partnered and unpartnered targets.

In 2007, as part of an investment deal with the Novartis Option Fund, Cequent gave Novartis an option to acquire the company's lead IBD candidate (see *RNAi News*, 6/21/2007). Under the terms of that arrangement, Novartis has three chances to exercise its option: upon selection of the lead target, after optimization of the drug candidate but prior to IND-enabling studies, or when the FDA gives the green light to a phase I study of the drug.

In September, Cequent announced that it had narrowed the list of potential IBD targets from eight to three, triggering an undisclosed milestone payment from Novartis (see *RNAi News*, 9/8/2008).

Fruehauf said last week that Cequent expects to have selected the lead IBD target "towards the middle of this year," but that it is also conducting preliminary work on 14 other targets for the indication, include three that are currently in *in vivo* testing.

These other targets, which are completely owned by Cequent, are expected to be the subject of partnering discussions that are likely to begin later in the year, he added.

Last year, Cequent President and CEO Peter Parker told RNAi News that, given the market opportunity for IBD treatments, the company was considering redirecting some of its resources away from an earlier-stage effort to develop a locally administered human papillomavirus treatment and toward IBD.

According to Fruehauf, the company has now done so and has "downgraded" the HPV program. IBD, he said, is "a big opportunity, and having FAP pave the way for oral applications [of the tkRNAi technology] makes it logical for us to have a [follow-up drug] candidate in the GI tract."