

BIOTECHNOLOGY

ACT Biotech Inc.

Oral kinase inhibitors for cancer

ACT Biotech Inc. is a new pharmaceutical company with a focus on oral kinase inhibitors for the treatment of cancer, but it has its roots in one of pharma's oldest players. Co-founder Ali Fattaey spent nine years, the last four as vice president of research, at Onyx Pharmaceuticals Inc., where he focused on kinase inhibitors.

Onyx had a long-lasting relationship with Bayer HealthCare Pharmaceuticals (a division of Bayer AG). "I knew the company really well, and our CEO had been a long-time executive at Bayer, so we had quite a few connections," Fattaey recalls. Those ties served him well when Bayer made the decision in 2006 to merge with Schering AG, and focus its oncology franchise on the cancer drug *Nexavar* (sorafenib), according to Fattaey. Many of Bayer's programs were suddenly available for out-licensing, and Fattaey negotiated a deal for the four programs in ACT's pipeline.

In 2008, Fattaey co-founded ACT Biotech with Wolf Busse, a long-time executive at Bayer who left in 2004 to found Bayer spin-off Aerovance Pharmaceuticals Inc. Bayer also invested in ACT, giving it an equity ownership interest in the company.

ACT Biotech's lead compound is telatinib, a potent and selective orally available inhibitor of three receptor tyrosine kinases: the vascular endothelial growth factor receptor (VEGFR), the platelet-derived growth factor receptor (PDGFR) and the KIT receptor. Based on *Ambit Biosciences Corp.*'s *KINOMEScan* screen, it is the most selective kinase inhibitor yet developed, according to the company. Its selectivity imparts an excellent safety profile, which makes it well tolerated at high, continuous doses. It also has no overlapping side effects with other chemotherapy drugs.

Those two characteristics make telatinib an intriguing candidate, says Fattaey. On the one hand, higher doses could give it increased efficacy as a single agent. On the other, the lack of side effect overlap means that it could be widely used in combination with other cancer therapies, including chemotherapy.

Due to its activity against VEGFRs, telatinib is likely a good candidate for renal cancer, because the VEGF pathway is often mutated in those tumors, according to Fattaey. The company has also noted activity in colorectal and stomach cancer. "Those two caught our attention based on Phase I clinical data. Both of those indications remain very high on our radar," Fattaey adds.

In fact, stomach cancer is the priority for telatinib. "The main reason is... we could go into frontline treatment. It showed good activity in Phase I trials, and it's a huge unmet need. There are no targeted therapies for stomach cancer, and it's one of the worst cancers that you can be afflicted with," says Fattaey.

There are three oral anti-angiogenic compounds that are FDA approved, but they have serious side effects in many patients, including skin reactions and hand-foot syndrome, characterized by redness, tenderness and sometimes skin peeling. Myelosuppression is another common issue. Telatinib doesn't cause either side effect, says Fattaey. "We think that its targeted selectivity profile is resulting in maintaining the same level of anti-angiogenic activity [as other agents] but reducing its side effects."

He believes that it compares favorably with some of the second-generation kinase inhibitors currently in development. "Looking at their kinase target pro-

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Business: Cancer drug development

Founded: February 2008

Founders: Ali Fattaey; Wolf D. Busse, PhD, CEO

Employees: 6

Financing to Date: \$18 million

Investor: NGN Capital LLC

Board of Directors: John Costantino (NGN Capital); Georg Nebgen, PhD (NGN Capital); Nils Behnke, PhD (Bain & Co.)

Scientific Advisor: Frank McCormick, PhD (University of California, San Francisco)

file, unfortunately they look a lot like the first-generation inhibitors. They tend to be more potent, but many have not addressed the selectivity issue. We'll have to see whether they can combine with chemotherapy as well as telatinib."

In colorectal cancer, telatinib is more likely to be a second line therapy in combination with chemotherapy, or third line as a monotherapy. Other possible indications include neuroendocrine tumors and hormone refractory breast cancer.

"It could be a backbone therapy for a number of different cancer indications because it could be combined with a standard of care therapeutic without bringing new toxicity. That unique ability to combine with chemotherapy is one of the major differentiating characteristics of telatinib," says Fattaey.

Telatinab received FDA orphan drug designation for treating gastric cancer in June 2010. The compound should finish a Phase II clinical trial by this August, and should go to Phase III testing this year in

combination with Roche division Genentech Inc.'s *Xeloda* (capecitabine) and cisplatin in the frontline treatment of stomach cancer, says Fattaey. If all goes well, the drug could be approved in 2014.

The company's second drug candidate, ACTB1003, targets downstream members of the phosphoinositide 3-kinase (PI3K) pathway and fibroblast growth factor receptors (FGFRs), which play important roles in cancer. It is also unusual among kinase inhibitors in that it induces apoptosis (programmed cell death) in tumor cells. Studies suggest that this activity is linked to the drug's inhibition of intracellular kinases called ribosomal S6 kinases (RSKs). "Because it's FGFR-specific, you can go into cancers with a high prevalence of FGFR mutations and alterations," which include bladder and endometrial cancers, says Fattaey.

"There is an amount of interest toward identifying FGF pathway inhibitors. Having one that also targeted RSK and induced apoptosis was very attractive for us," says Fattaey.

ACTB1003 will enter Phase I trials this year. Several cancers are known to have a high prevalence of mutations and alterations in the FGF receptors, including bladder and endometrial cancer. Both have significant unmet needs, and both have a high prevalence of mutations in FGFR2 and FGFR3. ACTB1003 targets both. Another possible indication is breast cancer, which can have alterations in FGF receptors as well as PI3 kinase. The Phase I trial will enroll patients with all three conditions.

There are other drugs that target FGF receptors, but "they don't induce apoptosis. Ours has a very unique profile," says Fattaey.

Currently marketed oral angiogenesis inhibitors include Bayer's *Nexavar* and Pfizer Inc.'s *Sutent* (sunitinib) as well as GlaxoSmithKline PLC's second-generation inhibitor *Votrient* (pazopanib). Others in development include Aveo Pharmaceuticals Inc.'s tivozanib and Pfizer's axitinib.

Telatinib has strong commercial potential. Stomach cancer alone has a global market of over \$1 billion, according to Fattaey.

He says it is too soon to provide a market estimate for ACTB1003, but its potential to induce apoptosis and independently target FGF receptors could enable its positioning as a single agent therapy in solid tumors. "It might be active as a single agent in indications where you don't usually see single agents like breast cancer. Its potential is beyond anything we've seen so far for major solid tumors like breast cancer. But we're also realistic. We'll take it into trials and then expand from there," says Fattaey.

ACTB1003's unique mode of action is an advantage, but it could pose some regulatory challenges. "It will be one of the first times that the agency would see a drug working with multiple modes of action. How do you best bring about those activities with the dosing and regimen? That will be an interesting regulatory path," says Fattaey.

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— JIM KLING