Drug companies look to biomarkers to salvage cancer target

The announcement last month that the biotech powerhouse Amgen was terminating a late-stage pancreatic cancer trial added another blow for drug developers hoping to halt tumor growth by blocking the protein known as insulin-like growth factor 1 receptor (IGF1R). In 2010, Pfizer abandoned its IGF1R-targeting antibody called figitumumab after phase 3 trials failed to demonstrate signs of clinical efficacy. And in the two years since, several other drugmakers have discontinued their own earlier-stage programs directed at the same target.

With the phase 3 failure of Amgen's ganitumab, "the field of IGF inhibition is at a crossroads," says Milind Javle, an oncologist at the MD Anderson Cancer Center in Houston who is running a clinical trial involving the Merck IGF1R blocker dalotuzumab. "This should serve as an example for us that we will not achieve success [with IGF1R inhibitors] unless we identify patients with predictive biomarkers who will benefit. There's really no alternative. We have to do it."

A promising potential biomarker that could help parse out patients who would benefit most emerged in July when a team led by Raju Kucherlapati, a cancer geneticist at the Harvard Medical School in Boston, published the largest genome-wide analysis of colon and rectal cancer to date. The group's analysis of 276 samples revealed that insulin-like growth factor 2 (IGF2)—a hormone that binds IGF1R to promote cell division—was overproduced in tumor samples from 22% of study participants (*Nature* **487**, 330–337, 2012). "We think that all of those 22% of the patients could benefit from the inhibition of either IGF2 or its receptor," Kucherlapati says.

However, the biomarker approach is far from a sure bet. In a study reported earlier this year at the American Society for Clinical Oncology meeting in Chicago, researchers found that people with colorectal cancers with high amounts of IGF2 responded badly to Merck's dalotuzumab. By comparison, people with the same tumor type showing elevated levels of a related protein, called IGF1, typically fared better on dalotuzumab than those without the predictive biomarker.

Given the mixed results to date, scientists say that more biomarker discovery trials are needed. Paul Haluska, an oncologist

Stop-work order creates uncertainty for Ebola drug research

The world's first major outbreak of Ebola hemorrhagic fever since 2009 raged across Uganda and Congo in July and August, killing at least 26 people. Despite this development, two biotech firms under contract from the US government to design drugs to treat people infected with the deadly virus could not purchase new research supplies or change the course of ongoing trials last month.

On 2 August, Massachusetts-based Sarepta Therapeutics and Canada's Tekmira Pharmaceuticals received a stop-work order from the US Department of Defense (DoD). Both companies are researching injectable drugs that block or interfere with the virus replication.

As *Nature Medicine* went to press, the military's Transformational Medical Technologies (TMT) office planned to "evaluate each contractor's efforts independently to determine the plan for moving forward with the development of the best drug candidate possible," Cicely Levingston, a DoD spokeswoman, told the journal in an email. However, despite a decision expected on 1 September, the nearly month-long pause has already created some uncertainty for future Ebola work.

Tekmira was in the middle of a phase 1 dosing trial to test TKM-Ebola, a small interfering RNA (siRNA) drug that works by binding and degrading the virus's RNA. Sarepta had planned to begin its dosing trial in August for its drug, called AVI-7537, which works by blocking a virus protein called vp24 crucial to the pathogen's replication.

Such human safety trials were the last step in the development of these agents under the US Food and Drug Administration's 'animal rule', which provides a path to drug approval for life-threatening agents where human efficacy trials aren't ethical or feasible.

Tekmira already demonstrated protection in macaques infected against an otherwise lethal dose of Zaire Ebola virus, a deadly strain that kills up to 90% of humans infected (*Lancet* **375**, 1896–1905, 2010). Sarepta reported similar results with AVI-7537 at this year's Oligonucleotide and Peptide Research, Technology and Product Development conference in Boston.

The DoD announcement in August to halt such work disturbed some in the field. "The stop-work order is a big issue because you are taking two of the three most promising technologies off the table temporarily," says Tom Geisbert, a virologist at the Galveston National Laboratory in Texas who has done research for Tekmira on TKM-Ebola.

A third option still in early stages of research, he explained, is a preexposure vaccine that relies on a recombinant vesicular stomatitis vector developed by Profectus BioSciences. The stop-work order has so far not affected Geisbert's research with the Maryland-based biotech on that vaccine concept funded by the US National Institutes of Health.

The timing of the DoD's stop-work order could not be worse, according to Chris Garabedian, president and chief executive of Sarepta. "This outbreak has raised concerns about US preparedness," he says. "The challenge we have with this virus is that it can be weaponized."

Since it was discovered in 1976, Ebola has killed almost 1,600 people, according to the WHO. Although commercial demand is low, outbreak threats are real, thus making the US military the likeliest manufacturer and potential buyer of any drug.

Garabedian notes that, if the stop-work period continues, Sarepta might be forced to shift some of its Ebola researchers to its Marburg virus drug development program, which is also completely funded by the DoD, but not affected by the order. He worries about the public health implications of such a move: "The most important thing is that work on the Ebola virus continues no matter what," he says.

Still, the firms' leaders voiced hope about the 1 September DoD decision. "If the stop-work order is lifted at that time, we are ready to move quickly and proceed with the TMT-funded work," Tekmira's vice president Ian MacLachlan wrote in an email to *Nature Medicine*.

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