

News

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Drug makers chase cancer stem cells

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As evidence implicating stem cells in cancer mounts, drug makers are taking notice. GlaxoSmithKline (GSK) in December formed a strategic alliance worth up to \$1.4 billion with OncoMed Pharmaceuticals, of Redwood City, California. The deal gives GSK an option to license four of OncoMed's antibody candidates developed to target cancer stem cells, one of which is scheduled to enter clinical trials in June.

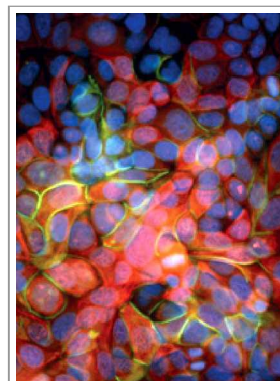
The GSK-OncoMed pact is the first major deal focused on cancer stem cell R&D, which is undergoing explosive growth. John Bates, the director of Biopharm Reports, in Cambridge, UK, says the number of companies devoted to this research has grown from 17 in April 2007 to nearly 40 today. What's more, patents covering developments in cancer stem cells doubled to about 70 in 2007, he adds. The problem is that not everyone even believes that targeting cancer stem cells will yield therapeutic benefits.

George Schreiner, CEO with Raven Biotechnologies in San Francisco, attributes the burst of commercial interest to recent evidence of cancer stem cells in solid tumors. Scientists have suspected since the 1950s that the cells play a role in blood tumors, such as acute myeloid leukemia, but their existence in solid tumors became evident only in 2003. That's when Michael Clarke, currently associate director of Stanford University's Institute for Stem Cell and Regenerative Medicine, and his then post-doc, Mohamed Al-Hajj, claimed to find cancer stem cells in breast tumors. The cells had two markers that are now synonymous with cancer stem cells: high expression of the antigen CD44 and low expression of antigen CD24. Isolated on the basis of these markers, the human cells were cultured and introduced into immunocompromised mice. Clarke and Al-Hajj found that only a few of the cells could spawn aggressive, metastatic tumors in the animals. Those findings bolstered a theory that solid tumors arise from a small population of cancer stem cells that, like normal stem cells, have the capacity for self-renewal. Clarke and his colleague Max Wicha, the director of the University of Michigan Comprehensive Cancer Center, founded OncoMed to pursue clinical opportunities in cancer stem cells in 2004. They now sit on the company's scientific advisory board.

Findings in other laboratories have since suggested cancer stem cells exist in various tumors, including those of the brain, head and neck, prostate, and colon. Scientists further postulate that cancer stem cells resist current drug therapies and repair DNA after radiation treatment more efficiently than their differentiated, daughter cells. That explains why solid tumors often recur after treatment, Schreiner explains. "What happens is the stem cells survive and repopulate to form a new tumor," he says. "And because they transmit their resistance to daughter cells, the new tumors are much harder to treat." Some researchers now believe the only way to cure cancer is by killing the stem cells that give rise to it.

OncoMed is one of a handful of companies preparing to test compounds against cancer stem cells in the clinic. In the GSK deal, OncoMed receives an undisclosed, up-front payment in cash and equity investment, with \$1.4 billion more tied to achieving milestones. Royalties on product sales would follow. OncoMed's lead candidate, a humanized monoclonal antibody (mAb) OMP-21M18, targets "a cancer stem cell pathway with broad applicability across multiple solid tumors," says Paul Hastings, the company's CEO.

Other companies preparing for clinical trials this year include Arius Research in Toronto, whose lead humanized IgG1 mAb targets a variant form of CD44 found in leukemia, breast, colon and prostate cancer cells. Also, Raven Biotechnologies has two mAbs in preclinical development: RAV17 (which targets the pancreatic assigned tumor marker PAN), which Schreiner says targets prostate as well as pancreatic cancer cells, and RAV18 (which targets ADAM-9), for colon and lung cancer. Raven is now preparing to merge with VaxGen, a San Francisco-based vaccine manufacturer, picking up needed cash reserves from a company with a depleted pipeline but plenty of manufacturing assets. Reflecting a broader trend in cancer drug development, most compounds targeting cancer stem cells are monoclonal antibodies, Bates says (see [Table 1](#)). MABs predominate because they target antigens on the cell surface rather than processes inside the cell as small molecules do.



Nancy Kedersha/Immunogen/Photo Researchers

How many of these breast cancer cells are stem cells driving malignancy?

Table 1: Selected anti-cancer stem cell treatments in development

[Full table](#)

The chief safety concern with targeting cancer stem cells, Clarke warns, is that these mAbs might also attack normal stem cells that replenish damaged tissues. "The main thing is to ensure that we eliminate the malignant cancer stem cells only without affecting the normal stem cells," he says. "Whether we'll be able to do this is the billion dollar question that everyone wants to answer."

Meanwhile, as commercial entities grow up around it, skeptics question the validity of targeting cancer stem cells. Current thinking holds that a tiny population of stem cells can explain why cancers recur even when existing treatments kill off up to 99% of a given tumor. According to Bert Vogelstein, a professor of oncology at Johns Hopkins University in Baltimore, tumors can be completely eradicated only if those small—and presumably drug-resistant—stem cell fractions are destroyed.

The tumor fraction contributed by stem cells ranges from a low of 0.1% to a high of 40%, and some reports have described tumors made entirely of stem cells. But Vogelstein also admits that if a tumor containing a large fraction of stem cells were almost completely eliminated by treatment, this would undermine the logic of targeting stem cells as the last, drug-resistant holdouts from which aggressive metastatic tumors would likely emerge refractive to treatment.

GSK's interest in OncoMed comes from a desperation "to tap into oncology space, an area in which it is particularly weak," says Sho Matsubara, an analyst with London-based Standard and Poor's Equity Research Division. Also, GSK's sales are assumed to decline in coming years, due to generic competition (Matsubara estimates a 7% drop annually for the next five years). It does have a compound of its own that may have shrunk breast tumors by attacking cancer stem cells. According to evidence described at the San Antonio Breast Cancer Symposium on December 17, six weeks' treatment with GSK's Tyverb (lapatinib), a small molecule used in conjunction with Xeloda (capecitabine) for late-stage breast cancer, slashed the number of stem cells by more than half among 30 women studied. Two-thirds of the women were reportedly cancer-free after follow-up treatment.

But others remain cautious as, in some instances, claims pointing to the existence of cancer stem cells have turned out to be wrong upon closer inspection. "More studies are needed to confirm that cancer stem cells were in fact targeted by Tyverb," Bates notes. "We need further evidence to show that cancer stem cells in humans have been fully characterized. And we need ways to demonstrate that a particular subpopulation of cells has been reduced by treatment," he notes.

Ultimately, the best evidence will come from more studies that show killing cancer stem cells improves patient survival, Bates says. For fast-moving cancers such as pancreatic tumors, the evidence may come sooner. In the case of slow-moving cancers, such as prostate, accumulating the necessary evidence could take more time, he points out.