

IN brief

Bush tails follow-ons

The legislation has yet to materialize, but observers suggest follow-on biologics are on the way. As part of the Bush Administration's budget message in February for fiscal year 2009, officials announced that they will seek "new statutory authority" to allow the Food and Drug Administration (FDA) to approve abbreviated applications for certain biologic products. Although some analysts expect that a crowded agenda and the distracting lead-up to presidential and congressional elections next November will keep Congress from making much headway, others say the "handwriting is on the wall," meaning the passage of such legislation is inevitable. Moving sooner rather than later may well benefit biotech companies, bringing a better deal for the industry than if deliberations and fine-tuning are postponed until after the November elections, some insiders point out. Exactly what those measures will be is still speculative: extended exclusivity is one possibility, clinical trials requirements for follow-on manufacturers another. Kathleen Jaeger, president and CEO of the Generic Pharmaceutical Association, warns that any such regulatory pathway should not be "filled with roadblocks to access, including excessive market exclusivity provisions." The pro-regulatory move by the Bush administration comes as something of a surprise. But anticipated cost-savings from 20 to 70% per product for generics, including biologic follow-ons, are both fiscally and politically valuable. *JF*

Amgen's Japan deal

Biotech giant Amgen, of Thousand Oaks, California, has sold off Japanese rights to develop and commercialize up to 13 molecules from its pipeline to Takeda Pharmaceutical for a combination of upfront payments, development funding and potential milestone payments that could total more than a billion dollars, plus royalties on product sales. The compounds include the epidermal growth factor receptor-targeting mAb Vectibix (panitumumab), biologics in oncology, inflammation, and neurology/pain, and the small-molecule angiogenesis inhibitor motesanib diphosphate, which Takeda will co-develop worldwide. "The development programs included in this collaboration represent the growth engine for Amgen in the next decade," states Amgen CEO Kevin Sharer. This cost-sharing move is in keeping with Amgen's streamlining of operations following a sharp drop-off in revenues from its Aranesp franchise, after regulators raised safety concerns around erythropoietin-stimulating agents last year (*Nat. Biotechnol.* **25**, 607, 2007). But Takeda's \$300 million upfront payment and \$340 million in defrayed R&D expenses won't boost Amgen's 2008 earnings, the company says. Eric Schmidt, senior research analyst at SG Cowen in New York, downplays the significance of the deal, which also includes the transfer of the shares of Amgen's 16-year-old Japanese subsidiary, Amgen KK. "[...] Royalties from Japan are likely to be modest," Schmidt says. "I don't see this deal as meaningful at all." *MR*

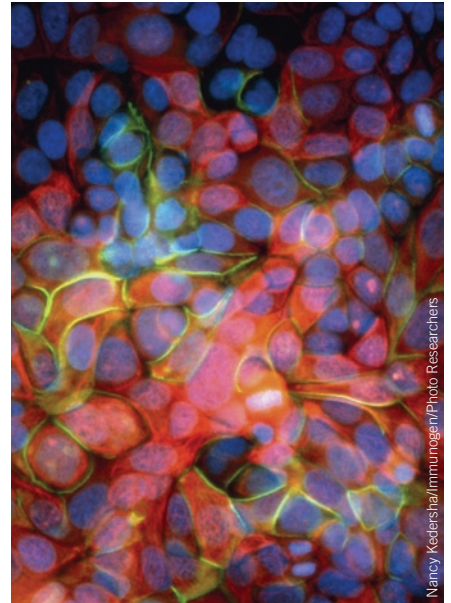
Drug makers chase cancer stem cells

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 treat-



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

ment 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

IN their words



"It's a way for farmers, and us, to make money, while doing something positive to help the environment."

Eric Rey, president and chief executive of Arcadia, which plans to reward Chinese farmers with carbon credits for growing

alanine aminotransferase transgenic rice that has enhanced nitrogen uptake and a lower requirement for fertilizer.

"When you think about gigantism in our business, the idea of 'big' and 'innovation' aren't two words you usually put together...there's a general belief that gigantism is antithetical to biopharmaceutical innovation."

Kevin Sharer, CEO of Amgen.

"This is really the first moonwalk for RNAi therapeutics."

John Maraganore, Alnylam's chief executive, on successful phase 2 results of the company's short-interfering RNA ALN-RSV01 against respiratory syncytial virus.

"We are an agency under assault. It will be difficult if this continues to attract the world-class scientists we need."

Janet Woodcock, recently appointed director of the FDA's Center for Drug Evaluation and Research, on the attacks that her members of staff have undergone over the years, causing some of the best scientists to leave the agency.

"I think this changed standards for all cancer medications.... [FDA's] Richard Pazdur said the reason [for approval] was that Avastin provided a direct clinical benefit. But that's progression-free survival. I have no idea, in fact, what that means...Maybe that's supposed to be a substitute for quality of life."

Breast Cancer Action's Barbara Brenner on the FDA's surprising decision to approve Avastin for metastatic breast cancer.

"I'd rather spend my money on my genome than a Bentley or an airplane."

Dan Stoicescu, a Swiss biotech entrepreneur (and millionaire), who has agreed to pay \$350,000 to startup Cambridge, Massachusetts-based Knome to map his genome.

New product approval

Humira (adalimumab)/Abbott Laboratories (Abbott Park, Illinois)

The US Food and Drug Administration has approved the drug Humira to treat moderate-to-severe juvenile idiopathic arthritis (JIA) in children aged four years and older. It is the first biologic treatment for JIA to be approved since 1999. Humira is already FDA-approved to treat adults with rheumatoid arthritis, Crohn's disease and psoriasis.

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.

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.

Charlie Schmidt Portland, Maine

Table 1 Selected anti-cancer stem cell treatments in development

Company	Lead product	Compound type	Status	Indication
GlaxoSmithKline	Tyverb (lapatinib)	Small molecule	FDA approved	Breast cancer
ChemGenex (Melbourne, Australia/Menlo Park California)	Omacetaxine Mepesuccinate	ND	Phase 2/3	Chronic myeloid leukemia
Geron (Menlo Park, California)	GRN163L	Small molecule	Phase 1/2	Chronic lymphocytic leukemia, solid tumors
Stemline Therapeutics (New York)	SL-401	Recombinant protein toxin	Phase 1	AML and myelodysplastic syndrome
OncoMed Pharmaceuticals/ GlaxoSmithKline	OMP-21M18	mAb	Preclinical	Multiple solid tumors
Raven/Vaxgen	RAV17/RAV18	mAb	Preclinical	Prostate and colon cancer
Arius Research (Toronto)	ARH460-16-2	mAb	Preclinical	Leukemia, breast, colon and prostate cancers
Immunocellular Therapeutics (Los Angeles)	ICT-111	Dendritic cell-based vaccine	Preclinical	Glioblastoma

AML, acute myeloid leukemia; mAb, monoclonal antibody. ND, not described.