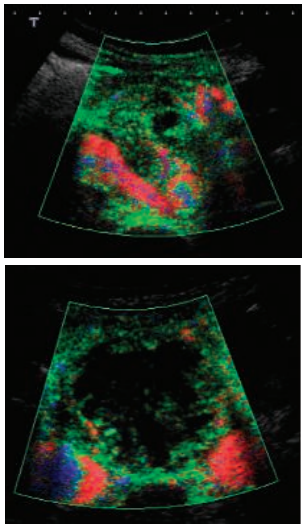
Encouraging Results for Second-Generation Antiangiogenesis Drugs

The strategy of denying growing tumors a blood supply continues to show clinical promise as new and improved drugs move through the pipeline

The development of cancer drugs that stifle tumor growth by blocking the formation of the blood vessels they need seems to have turned the corner. Early last year, the U.S. Food and Drug Administration approved the first cancer drug, an antibody called Avastin, that is specifically designed to prevent this tumor angiogenesis, as the new blood vessel growth is called. Avastin may soon have company, if presentations last week at the annual meeting of the American Society of Clinical Oncology (ASCO) in Orlando, Florida, are any indication.

One advanced clinical trial showed that a new antiangiogenesis drug called sorafenib significantly slows metastatic kidney cancer, and another drug, known as Sutent, proved its mettle in treating a digestive system cancer called GIST (gastrointestinal stromal tumor). In contrast to Avastin, which must be injected because it's a protein, both of these drugs are small molecules that can be taken in pill form. Perhaps even more important, the new drugs take aim at multiple molecular targets, only some of which are related to blood-vessel growth. The results from this novel drug class "mark the dawn of a new era in antiangiogenesis therapy," says William Li, director of the Angiogenesis Foundation in Boston, Massachusetts.



Slow flow. Blood flow to a kidney tumor (*top*, green) is reduced (*bottom*) by an angiogenesis inhibitor.

Despite their chemical differences, Avastin and the new drugs share a common purpose: starving tumors of blood. Avastin is designed to bind to and block the activity of an angiogenesis-promoting protein called vascular endothelial growth factor (VEGF). Sorafenib, which is being developed by Bayer Corp. and Onyx Pharmaceuticals, and Sutent, under development by Pfizer Corp., also block VEGF action, but in a different way. The receptors through which VEGF works are so-called tyrosine kinases, which add phosphate groups to certain proteins. The new drugs block this kinase activity, thus inhibiting receptor action.

In addition, they inhibit other tyrosine kinase enzymes within cells. This means the drugs may block tumor cell growth directly, as well as by inhibiting angiogenesis. "These are like Gattling guns; Avastin is like a sniper," is how Li puts it.

Sorafenib was originally identified on the basis of its ability to inhibit a tyrosine kinase called Raf, a member of a major cellular growth control pathway—one that often contributes to the runaway cell division of cancer cells due to mutations that cause it to be overactive. But the drug also inhibits additional tyrosine kinases, including the receptors for VEGF and for platelet-derived growth factor (PDGF) and the products of the *KIT* and *FLT-3* oncogenes.

Sorafenib, which was discovered 4 years ago, moved quickly through animal and preliminary clinical studies. By early 2004, investigators had begun a large phase III trial of the drug's effectiveness in patients with metastatic kidney cancer. This double-blind trial included some 900 patients at multiple medical centers who had not responded to previous therapy and who were given either sorafenib or a placebo.

At the ASCO meeting, Bernard Escudier of the Institute Gustave Roussy in Villejuif, France, reported that sorafenib "very significantly" increased the length of time before the treated patients' cancers grew visibly, from 3 months in the placebo group to 6 months. "This was the best data we have seen in kidney cancer with any drug so far," Escudier says. The improvement was so striking that the review committee for the trial unblinded the results early so that the controls could also receive the drug.

Despite the drug's targeting of multiple tyrosine kinases, side effects, which included rashes, hair loss, nausea, diarrhea, and high blood pressure, were relatively mild. Still to be determined, however, is whether the delayed progression will translate into improved survival for the patients. But periodic imaging of the tumor's blood flow did suggest that at least part of sorafenib's effects were due to its ability to block angiogenesis. "Tumor vascularization was decreased" in patients who received the drug, Escudier says.

Sutent, identified about 5 years ago by Julie Cherrington, then at SUGEN Inc. in South San Francisco, California, and her colleagues, is also moving quickly through clinical testing. (SUGEN has since been acquired by Pfizer.) This drug also targets a broad set of tyrosine kinases. The fact that it inhibits the protein produced by the *KIT* oncogene suggested that it might be a good drug for treating GIST. "GIST cells are totally addicted to that [KIT] signal" for growth, says George Demetri of Harvard's Dana-Farber Cancer Institute in Boston, who led the phase III clinical trial of Sutent for GIST reported at the meeting.

One proof of that came with the discovery that this kind of tumor responds to the anticancer drug Gleevec, which inhibits both KIT and another kinase that drives a leukemia called CML. The current trial included more than 300 GIST patients for whom Gleevec no longer worked. Again the results were so striking that the trial was unblinded early so that the controls could receive treatment.

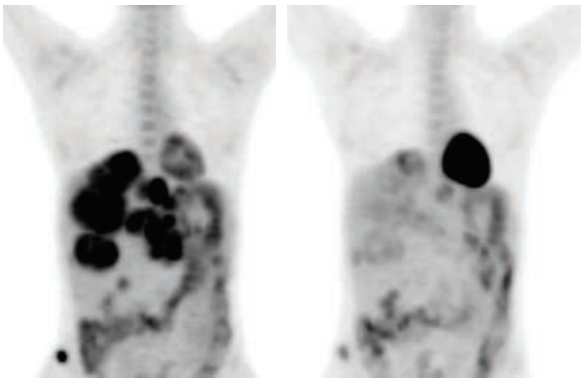
Sutent delayed the time of tumor progression on average from 1.5 to 6.3 months and also significantly reduced the death rate, even at this early stage of analysis. And like sorafenib, Sutent may be effective against kidney tumors. Robert Motzer of Memorial Sloan-Kettering Cancer Center in New York City described the results of two smaller studies, including 169 patients with metastatic kidney cancer. Roughly two-thirds of the patients responded to the drug with either tumor shrinkage or delayed progression.

In addition, Kathy Miller of Indiana University, Indianapolis, reported that in a small phase II trial, about 14% of breast cancer patients who failed previous chemotherapy treatments responded to Sutent. "It doesn't sound like much, but in this group of heavily pretreated patients, this is very good," she says.

Not all the large studies of second-generation antiangiogenesis drugs reported at ASCO produced clear results, however. The drug known as PTK/ZK, which is being developed by Novartis and Schering, targets most of the same tyrosine kinases as sorafenib and Sutent. Although it did produce a 12% increase in progression-free survival in a trial including nearly 1200 patients with metastatic colon cancer, that improvement did not attain statistical significance.

As for Avastin, the first-generation angiogenesis inhibitor continues to show promise. Although it is currently approved only for treating colon cancer, results pre-

sented at the ASCO meeting show that when given with more conventional chemotherapeutic drugs, Avastin can work on other cancers as well. In an earlier trial on patients with advanced breast cancer, Avastin combined with chemotherapy did not produce a statistically significant improvement over the results of chemotherapy alone. But at the meeting, Indiana's Miller, who also led the earlier study, reported on a new phase III trial in which Avastin was combined with the chemotherapy drug paclitaxel. This time, the news was good. Patients who got both drugs experienced significant increases in progression-free survival and overall survival compared to those on paclitaxel alone.



Quick reaction. A gastrointestinal tumor (*left*, dark areas) rapidly shrinks (*right*) after 1 week of treatment with the drug Sutent.

Avastin may have worked better this time, Miller says, because those in the current trial had not previously been treated with chemotherapy and thus their cancers may have been less advanced than those in the earlier trial, who had all undergone—and failed—several rounds of chemotherapy. Genentech, the company that makes Avastin, got other good news at the ASCO meeting. In another phase III trial, described by Alan Sandler of Vanderbilt University School of Medicine in Nashville, Tennessee, the addition of Avastin to a chemotherapy regimen slowed tumor progression in patients with one form of nonsmall cell lung cancer.

Although second-generation antiangiogenesis drugs such as sorafenib and Sutent, unlike Avastin, have shown promise when given alone, researchers are also beginning to test the drugs in combination with other therapies. The idea, they say, is to mix drugs that hit different aspects of the pathological changes that drive tumor growth. An antiangiogenesis drug might be combined, for example, with a drug that blocks the cell growth–stimulating activity of epidermal growth factor. "We're getting smarter," Demetri says. "We're going to be able to profile the tumor and pick and choose [anticancer] drugs just like we pick and choose antibiotics for treating life-threatening infections." –JEAN MARX

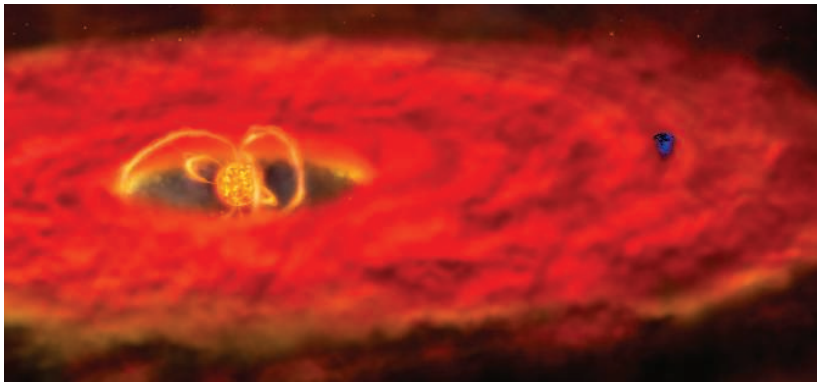
Astronomy

Turbulent Orion Nebula Shows A Flare for the Dramatic

A deep x-ray scan of a crowded star-forming cloud suggests that our solar system's youth was far from serene

On crisp winter nights, the stars of Orion, the Hunter, rule the Northern Hemisphere's sky. But deep within the Orion Nebula, the constellation's famous stellar nursery, conditions are anything but chilly. Fierce and persistent flares from baby stars pierce the nebula with x-rays, according to unprecedented studies released this month. The spasms light up the cloud "like an x-ray Christmas tree flashing on and off," says astronomer Eric Feigelson of Pennsylvania State University, University Park.

The pyrotechnics were revealed by the Chandra Orion Ultradeep Project (COUP), in which NASA's Chandra X-ray Observatory stared at the nebula for nearly 2 weeks in January 2003. The penetrating scan captured the early lives of more than 1400 young stars, ranging from titans to dwarfs. The results turn back the clock to the infancy of our own sun, which may have formed in a similar nursery 4.6 billion years ago among siblings that have long since dispersed.



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Magnetic turmoil. Giant flares may spark turbulence in disks around newborn stars.

COUP's international team of 37 scientists, led by Feigelson, found that the eruptions unleashed by Orion's stars are thousands of times stronger than the worst our sun can dole out today. The biggest flares probably extend out far enough to strike the disks of gas and dust around the young stars from which planets may form. No one knows the impacts of such giant magnetic short-circuits. But in one intriguing scenario, they churn circumstellar disks enough to keep newborn planets from spiraling into their suns.

If that happened in our solar system's youth, it would be an ironic twist on our conception of x-ray flares as dangerous, Feigelson says: "They may have protected Earth from early destruction."

This statement became the catch phrase of a NASA briefing for reporters on 10 May, even though it stretches current theory, Feigelson readily admits. But for the first time, he says, the 13 papers* from COUP give theorists the data they need to understand the full range of high-energy tantrums from the youngest stars.

The perfect target

The Orion Nebula is ideal to study so many stars in one fell swoop, says astrophysicist Fabio Favata of the European Space Agency's R&D center ESTEC in Noordwijk, the Netherlands. "If you were to design a nebula from scratch as a target for

* To appear in *Astrophysical Journal Supplement Series*, available at www.astro.psu.edu/coup