to heart and regularly performs PRAs on the shuttle's systems and the shuttle as a whole. In 1995, the overall calculated value for catastrophic shuttle failure was 1 in 145; in 1998, that value dropped to 1 in 245, due, in part, to design improvements of the main engines. Another PRA, started before the accident, is under way.

But as the Columbia disaster showed, the latest number appears to be wrong. According to Rutledge, these overall risks are inherently deceptive. "There's all sorts of complexity that we may not be able to capture," he says. Overlooking a possible source of failure often leads to an underestimate of risks, as does ignoring the possible dependence of failures of different systems, which can boost the risks immensely. Furthermore, these analyses tend to ignore human fallibility. "People under time constraints are going to cut corners," says Paté-Cornell. But, notes Rutledge, there is pressure to generate a single number. "[The public] likes to know one number, and people on Capitol Hill like to know one number, so we have it," he says. But inside analysts don't put much stock in such a figure.

So what are PRAs good for? "The relative risks are what's really important," says Stamatelatos. By assessing which risks are more likely to cause failure than others, NASA can direct its limited resources to the problem areas. "These efforts help us make upgrades and project the safety of the shuttle into the future," Stamatelatos adds. According to Mosleh, NASA is working hard to make PRAs more accurate by taking into account the changing conditions as the shuttle flies; in the meantime, the risk assessments already performed are helping investigators generate a fault tree to study what might have gone wrong with Columbia.

But even the most sophisticated PRA is likely to be wrong when it comes to calculating the absolute odds of a rare event such as a shuttle failure. "The only way you can calculate this is by modeling," says Stamatelatos. Adds Rutledge, "The exact number is unknowable."

–CHARLES SEIFE

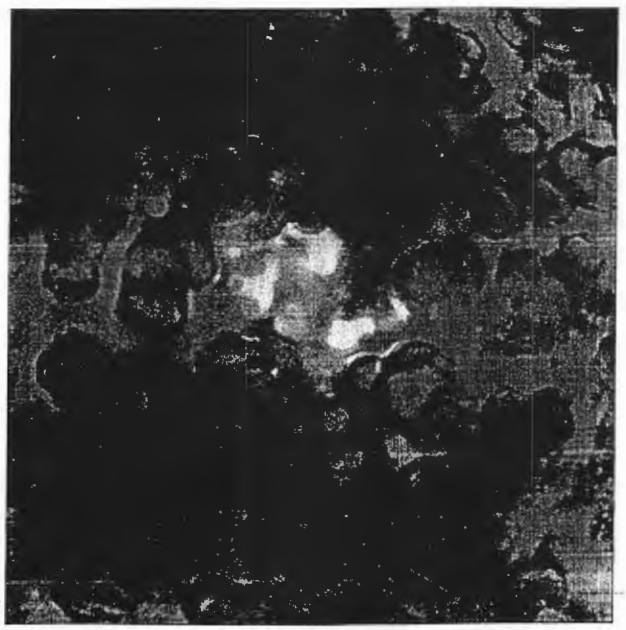
Medicine

Tracing the Steps of Metastasis, Cancer's Menacing Ballet

New studies are beginning to deconstruct this mysterious process, which is overwhelmingly the cause of cancer deaths

"We put the cancer cells in last Tuesday," Weili Fu explains, as she slits open a mouse's chest. Speaking over the rapid hiss-click of a miniature ventilator, she threads a tiny catheter into the pulmonary artery and infuses a bolus of dye. Fu and her mentor at the University of Pennsylvania in Philadelphia, Ruth Muschel, keep the lung pressure high until the chemical runs through, highlighting the lungs' blood vessels to help trace the path of human cancer cells injected 8 days ago into the animal's tail. Under a microscope, the tumor cells show up in vivid shades of yellow within blood vessels dyed red—exposing a dynamic view of metastasis, the process by which cancer cells migrate from a primary tumor to other sites in the body.

When cancer cells metastasize, the fallout is devastating; indeed, it leads to death for most of the 282,000 people in the United States who succumb to four common cancers—of the breast, lung, prostate, and colon. But until very recently, many biologists were put off by the challenge of studying this process in the lab. The roadblocks are daunting. Because metastasis sweeps through various parts of the body, it must be studied mainly in whole animals rather than in cell and tissue cultures. Obtaining data from mice, which rarely have cancers that spread, remains difficult. Human tissue samples are scarce, too, because few cancer patients have secondary tumors surgically removed.



Illuminating an enemy. Cancer cells glow yellow inside the blood vessels of a mouse's lung.

CREDIT: WEILI FU AND RUTH MUSCHEL; ILLUSTRATION: C. SLAYDEN/SCIENCE

Although these challenges persist, the study of metastasis is undergoing a renaissance. Once the province of a small band, it is now drawing many scientists as one of the last great frontiers of cancer biology. Recent studies have found, unexpectedly, how little in metastasis occurs by chance. Instead, a constellation of molecular signals in cancer cells and the patient's own body steer tumor cells, bit by bit, from the primary site to a new, ideal home. Large-scale gene studies are suggesting fundamental differences between metastatic cells and other cancer cells. Researchers are also taking a deeper look at electrifying similarities between embryonic and metastatic cells.

Deciphering metastasis is a painstaking task. Like Muschel and Fu, growing numbers of researchers are tackling complex experiments and obtaining images of disease that could open new opportunities for treatment. The field's expansion has also brought growing pains. New entrants are challenging long-accepted theories, leading, many say, to sniping and quarrels, as each camp seeks to advance its worldview (see sidebar, p. 1005).

Although contentious at times, this work is providing insight into some fundamental puzzles. Among them: Are certain tumors predestined to be metastatic from their very beginning? What draws cancer cells to specific organs? Ultimately, for a cancer to progress, "something has to happen" to give tumor cells the capacity to thrive in new environments, says Bruce Zetter of Children's Hospital in Boston, and researchers are still trying to learn what that is.

A cunning enemy

Viewed in retrospect, the spread of cancer looks like an intricately choreographed ballet, linking dozens of steps in what's known as the metastatic cascade. Before they form a new tumor, cells must escape from the primary site, tumble into the bloodstream, and survive typhoonlike blood flow powerful enough to kill them. They must lodge in a spot conducive to growth (most are not) and colonize this outpost, recruiting blood vessels critical for nourishment.

This pattern—well established and orderly though it may seem—belies a number of peculiarities familiar to oncologists. Tumors that appear identical under the microscope display utterly divergent behaviors in the body, some spreading aggressively while others stay put. Cancers that appear cured may never stir again; or they may resurface as a metastasis 10 or 20 years later. This unpredictability frustrates physicians and patients.

One of the enduring goals of the field is to find a way to read a cancer's tea leaves. Yet even as sophisticated diagnostics push back the date when cancer first becomes visible, no universal signs of cell destiny have emerged. "When you try to ask the question of whether early detection by mammography predicts outcome," says Muschel, "it's not very good. That could be because there are two categories of tumors, one of which has the metastasis phenotype." If those phenotypes exist, identifying them could potentially guide treatment decisions.

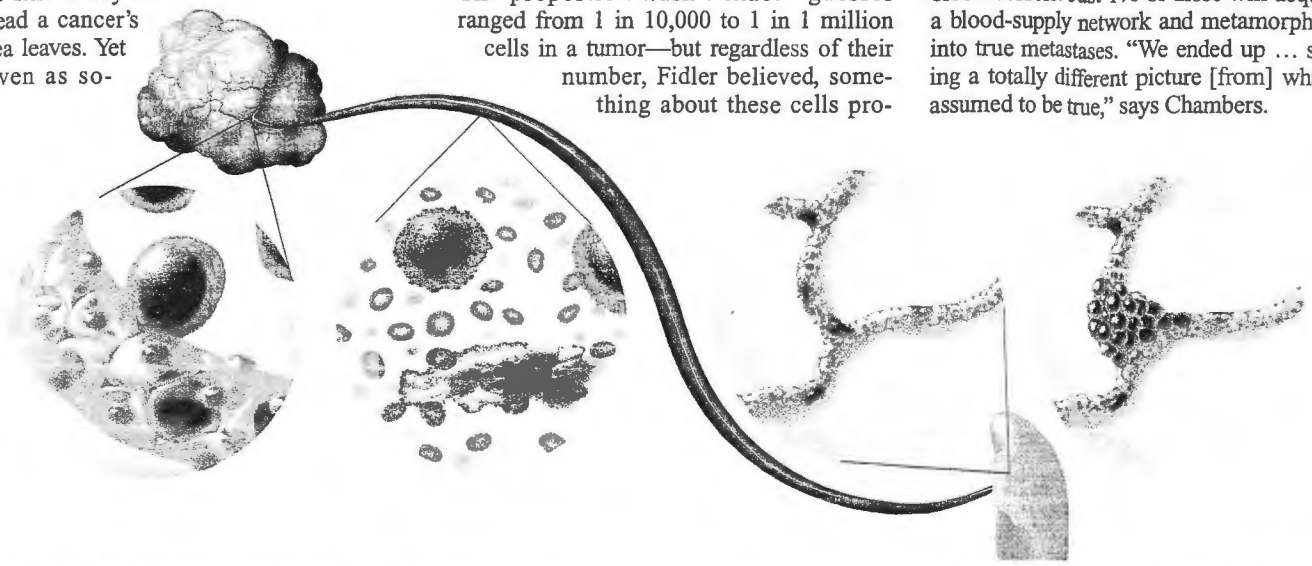
Scientists have not unearthed a global signature that reads "metastasis" from the day of diagnosis, but they are picking up messages from all sorts of cancer cells that hint at their destiny. From one overexpressed enzyme marking metastatic colon cancer cells to a dizzying expression pattern of 70 genes in breast cancer linked to a poor prognosis, researchers are discerning individual, and sometimes divergent, signatures that are gradually pointing the way toward metastasis predictors.

What makes a metastasis?

In the early days of metastasis research in the 1970s, the focus was on dissecting the first step in the metastatic cascade, a cancer cell's escape from the primary tumor. At that time, scientists believed that if cancer cells had peeled off and infiltrated the bloodstream, "the horse is out of the barn and there's nothing you can do about it," says cancer biologist Carrie Rinker-Schaeffer of the University of Chicago. Isaiah Fidler, a veterinary surgeon–turned-pathologist, proposed 3 decades ago that a cryptic minority of cancer cells harbor an inherent ability to spread. The rest are ill equipped to travel, said Fidler, now at the University of Texas M. D. Anderson Cancer Center in Houston. The proportion wasn't exact—guesses ranged from 1 in 10,000 to 1 in 1 million cells in a tumor—but regardless of their number, Fidler believed, something about these cells propelled them to launch a metastasis.

Fidler, widely considered the grandfather of metastasis research, inspired a core group of fewer than a dozen scientists to roll up their sleeves and try to identify what makes these cells different from others in the primary tumor. They focused on genes that are turned on or off only in cancer cells that have metastasized. Patricia Steeg of the National Cancer Institute in Bethesda, Maryland, and colleagues found the first gene, *nm23*, in 1988; at least seven more have been identified since then. When turned on, these genes appear to inhibit cancer's spread; when shut down, they are often associated with metastases, but apparently they do not affect primary tumor growth. Researchers dubbed them metastasis-suppressor genes, although their precise functions remain fuzzy. At a meeting in the late 1990s, Steeg and her colleagues, pooling their information, discovered that metastasis-suppressor genes are less relevant to the first stage of the metastatic cascade than to one of the last, a cancer cell's ability to colonize a new site.

This realization came as other researchers, eager to find out what enables a small fraction of malignant cells to thrive, began to focus on the later steps of the cascade. To their surprise, scientists are discovering that metastasis faces remarkably long odds. Although some tumors shed millions of cells into the blood, few reach an organ, and even fewer grow into full-blown secondary tumors. Recent imaging work in Ann Chambers's lab at the University of Western Ontario in London, Canada, has shown that only 1 in 40 skin cancer, or melanoma, cells that hit the liver will form what are called micrometastases: clumps of cells that remain small unless they develop blood vessels. Just 1% of those will acquire a blood-supply network and metamorphose into true metastases. "We ended up … seeing a totally different picture [from] what I assumed to be true," says Chambers.



Tumbling down the metastatic cascade. After breaking off from the primary tumor (far left), cancer cells travel through the blood vessels. Those that reach a secondary site such as the lung (right) may colonize it and form a metastasis.

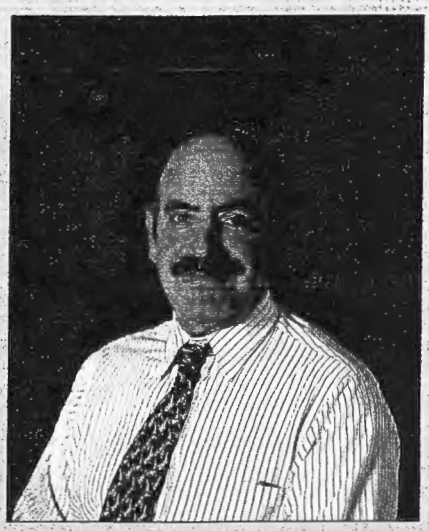
What enables a voyaging cancer cell to beat the odds and thrive? Metastasis researchers have more than one explanation. Some, such as Steeg and Rinker-Schaeffer, believe that metastasis-suppressor genes, which seem to come into play later in the cascade, are critical. They agree with Fidler's original theory that only a tiny portion of a primary tumor contains cells with metastatic potential. This suggests that the larger the tumor, the likelier it is to harbor metastatic cells and hence to spread.

Although Fidler's theories have been challenged in the past, it's only now, with the advent of gene microarrays, that they are being rigorously put to the test. Todd Golub, head of cancer genomics at the Whitehead Institute in Cambridge, Massachusetts, runs

A Clash Over Genes That Foretell Metastasis

Biologists who sift DNA for evidence of what causes cancer cells to become metastatic are torn between two camps. One holds that a fatal problem occurs relatively late, when so-called metastasis suppressor genes fail, allowing an existing tumor to spread. About eight candidate genes fitting this scenario have been identified (see main text).

But a second group remains unconvinced. These researchers hold that the same genes that drive primary tumors—oncogenes and tumor-suppressor genes—also launch metastatic cancer, and that even small primary tumors can contain mostly metastatic cells. Metastasis, they argue, is not genetically distinct; it is just the final step of well-studied processes of cell dysregulation.



Doubter. The Whitehead Institute's Robert Weinberg raises questions about the genes behind metastasis.

This debate erupted in a heated exchange of comments last summer after Robert Weinberg, a lion of molecular oncology studies, staked out a position against a unique role for metastasis-suppressor genes. A member of the Whitehead Institute and professor at the Massachusetts Institute of Technology in Cambridge, Weinberg and his former postdoc René Bernards, now at the Netherlands Cancer Institute in Amsterdam, argued in the 22 August 2002 issue of *Nature* that some of the initial mutations that transform a normal cell into a cancerous one can also cause metastasis. They specifically pointed to the oncogenes *ras* and *myc*, which Weinberg has studied for much of his career.

The article struck a nerve. "We got both love and hate letters," about 60 in all, says Bernards. Weinberg has been here before: In the 1980s, his lab discovered what it thought was a metastasis gene before finding that it didn't cause metastasis after all.

Advocates of the metastasis-suppressor theory say that Weinberg and Bernards have slighted their work. "The metastasis people who've toiled in the trenches ... have long felt that oncogenes and tumor suppressors get all the limelight," explains one researcher who straddles both camps, Bruce Zetter of Children's Hospital in Boston. Others are less diplomatic. The paper "completely ignores a body of literature" on the role of metastasis-suppressor genes, fumes cancer biologist Carrie Rinker-Schaeffer of the University of Chicago.

Weinberg's greatest allies may be those who have identified genetic signatures in primary tumors that appear to anticipate metastasis. Todd Golub, a Whitehead colleague of Weinberg's who published a paper in *Nature Genetics* in December postulating a 17-gene signature in primary tumors that could predict metastasis, agrees with Weinberg's theory. His own work, he says, supports the view that a tumor's destiny is carved out early on, and that in these cases, metastatic cells come to dominate a primary tumor. Another supporter is Robert Kerbel of the Sunnybrook and Women's College Health Sciences Centre in Toronto, who predicted something similar in the 1980s.

For his part, Weinberg protests that his article was misunderstood, and that he wasn't denying the existence of metastasis-suppressor genes.

The ruckus over the article has some experts calling for calm. "I sound like a U.N. diplomat, ... [but] there's room for everyone," says Kerbel. Indeed, even the combatants concede that the two camps may be talking about overlapping sets of genes.

–J.C.

one of many cancer labs that are developing microarray technologies to monitor thousands of genes simultaneously. Studies analyzing tumor samples and correlating patient outcomes with gene activity are identifying literally dozens of genes whose expression appears to vary in tune with cancer's spread.

Researchers such as Golub and René Bernards of the Netherlands Cancer Institute in Amsterdam argue that certain primary tumors are, early in development, composed largely of cells with a genetic makeup that compels them to metastasize. Furthermore, they believe it may be possible to identify these deadly tumors early on by analyzing their gene-expression patterns.

Seeds and soils

As scientists skirmish over gene-expression studies, separate molecular biology work is spawning at least one principle on which almost everyone agrees: Metastasis appears to be partly controlled by messages embedded in the organs to which cancer spreads. Elements of the signals stimulating metastasis may come "not from the tumor cells themselves but from the microenvironment," suggests Golub. The new tumor locale seems to include a key that cancer cells use to unlock the site and thrive.

Researchers have long puzzled over the ties that bind metastasized cancer to certain organs, knowing that specific cancers indisputably show a taste for specific sites. Whereas breast cancers favor the bone and lungs, for example, colon cancers prefer the liver. In 1889, a British surgeon named Stephen Paget spelled out in *The Lancet* his "seed and soil" theory, which argues that metastasis depends on matching certain types of "seeds," or cancer cells, with "soils" in which they are likely to grow. Researchers now agree that although many ties between primary tumors and metastases are statistically predictable based on blood-flow patterns, about a third defy logic, among them breast and prostate cancers' frequent and deadly spread to bone.

As they decipher these affinities, biologists are finding that the choice of where to relocate isn't solely a cancer cell's to make: Distant organs also beckon them. The ensuing dialogue tugs the cells closer, or creates a welcoming second home in which they can freely multiply.

Albert Zlotnick, director of genomic medicine at Eos Biotechnology in South San Francisco, California, saw this pattern emerge 2 years ago while examining well-known proteins called chemokines. Chemokines, which recruit white blood cells to damaged tissue, landed in the spotlight in 1996 when HIV was found to use them to enter cells. Zlotnick eavesdropped on chemokine signals between metastatic breast cancer cells and two locales to which breast cancer spreads, lymph nodes and lungs. He was surprised to find that chemokines helped explain breast cancer's affinity for these organs: The cancer cells expressed specific chemokine receptors, and lymph nodes and lungs expressed the molecules that bind to them. In mice, he found, blocking this back-and-forth Morse code helped inhibit cancer's proliferation.

Joan Massagué, a new entrant to the metastasis field, is exploring what drives breast cancer to distant targets, particularly bone tissue. The question is especially intriguing because breast cancer cells strike bone more readily than anatomy would pre-

dict. In his lab at Memorial Sloan-Kettering Cancer Center in New York City, Massagué is studying how the cancer and target cells signal to one another; already, he's identified proteins that enable cancer cells to adhere tightly to bone and attack bone tissue.

Massagué is also finding that breast cancer cells corrupt a much-studied signaling pathway called transforming growth factor–β (TGF-β). Other researchers have found that TGF-β can function as a tumor suppressor, slowing the growth of some primary tumors. But in unpublished research, Massagué has observed that metastatic breast cancer cells appear to turn the tables on TGF-β; for them, it helps spur invasion and metastasis. Cancer cells must "acquire a number of abilities … to nest and thrive at appropriate sites," says Massagué, and he thinks that subverting TGF-β is one of their successful dodges.

Some cutting-edge work also suggests that cancer cells master these tricks by turning back the clock. Last month, Denise Montell, a developmental biologist at the Johns Hopkins School of Medicine in Baltimore, Maryland, published an article in *Nature Reviews: Molecular Cell Biology* pointing out a possible connection between embryo development and metastasis that she stumbled on by accident. Montell was analyzing how cells in an adult fruit fly ovary migrate from one place to another—similar to the cell migration that occurs during embryo development and during metastasis, when cells move from one organ to another.

Montell found that two critical cell-signaling pathways, known to help cells proliferate in embryos and, in some cases, in cancers, also confer mobility. One of these, governed by steroid hormones and a fruit fly gene called *taiman*, controls the timing of cell migration in certain ovarian and embryonic cells. A closely related mammalian protein is highly expressed in metastatic breast cancer. Although scientists have long linked hormonal effects with cancer, they have not coupled hormones with migratory abilities. Startled by these associations, 2 years ago, Montell shifted some of her 10-person lab into metastasis studies and collaborations with cancer biologists.

Others are seeing tantalizing parallels between early development and cancer cells that have completed the metastatic cascade. "If you look at the molecular profile of these cells" in gene-expression studies, "they look like stem cells," says Mary Hendrix of the University of Iowa in Iowa City. Stem cells carry built-in blueprints that enable them to morph into various tissue types. This, she explains, would clarify how breast cancer cells can live perfectly comfortably in strange environments.

All these advances, though, are years from being translated into therapies. Adding to the uncertainty is the erratic performance of one treatment that targets metastases as well as primary tumors: antiangiogenic drugs, which inhibit new blood vessel growth (*Science*, 22 March 2002, p. 2198).

But if old treatment approaches are struggling, new ones are emerging. Researchers are increasingly interested in designing drugs to focus on the final step in the metastatic cascade. Tumors have often spread insidiously through the body by the time they are diagnosed, but as surgeon Judah Folkman of Children's Hospital in Boston has shown, micrometastases may linger for anywhere from a few months to more than a decade before suddenly becoming metastases proper. This suspended state has recently captured scientists' attention; many believe that it's a pause that offers hope, and prolonging it may be the best short-term strategy for halting metastasis.

Delaying disease may defeat it. "That, I think, is a newly appreciated goal of cancer treatment," says Zetter of Children's Hospital. He hopes that someday metastasis, if not curable, will be treatable as a chronic disease—and that more than just a lucky few will be able to live with it.

–JENNIFER COUZIN

Genomics

Tinker, Tailor: Can Venter Stitch Together a Genome From Scratch?

J. Craig Venter plans to create microbes to cure the world's environmental woes. Whether he can even partially succeed is an open question

Craig Venter can't stand to be bored. No sooner had he and his team at Celera Genomics finished sequencing the human genome than Venter set another modest challenge for himself: He would tackle the world's environmental woes. His self-proclaimed goal (which landed him in newspapers and magazines around the world a few months ago) is to create microbes from scratch that can produce clean energy or curb global warming. To make this a reality, he set up a new organization, the Institute for Biological Energy Alternatives (IBEA) in Rockville, Maryland, right next to The Institute for Genomic Research that he founded in 1992. He got a small vote of confidence last November, when the Department of Energy awarded IBEA $3 million to take the first few steps toward that goal.

> "How do you boot up a new genome?"
> –BERNHARD PALSSON

Venter predicts he will pull off the first step—creating a synthetic genome that, when inserted into a cell, can live and replicate—within 3 years. But experts on microbes and genomics are not so sure. No one has ever synthesized a string of DNA hundreds of thousands of base pairs long, much less "brought it to life." Obstacles range from determining which genes are essential to how to switch on a new genome. As for going the next step and creating a new pollution-fighting bug, many dismiss the scheme as science fiction or, at best, decades away.

But Venter's critics and champions are closely watching what happens to the synthetic genome. "If he does make it, it will be a momentous achievement," promising insights into the fundamental workings of all living things, says Eugene Koonin, an evolutionary biologist at the National Center for Biotechnology Information in Bethesda, Maryland.

Step one

Venter's project has its roots in the mid-1990s, when he and his colleagues sequenced the peculiar genome of *Mycoplasma genitalium*, a species of bacteria that lives in the human urinary tract. They discovered that *M. genitalium* has only 517 genes, making it among the smallest genomes known (*Science*, 20 October 1995, p. 397). Its tiny size raised some fundamental questions, says Venter: "Is there a smaller set [of genes] we don't know about? Is there a way we can define life at a molecular level?"

To find out, Venter joined up with Clyde Hutchinson of the University of North Carolina, Chapel Hill, and other researchers to test whether individual genes were essential for *M. genitalium*'s survival in the lab. They would knock out a gene, watch the microbe thrive or wither, and then repeat the experiment with a different gene. A surprising number of genes turned

CREDIT: MARTY KATZ