"transmembrane 4" (TM4) family, which is so called because all its members—now numbering about 15—have structures suggesting that they weave through the outer cell membrane four times. Because the TM4 family is only a few years old, researchers are just beginning to learn what its members do. "There is no definitive biological understanding of what any of this extensive family of proteins is doing," says cell biologist Martin Hemler of Harvard Medical School, whose own work recently intersected with the TM4 family.

But circumstantial evidence suggests that the TM4 group might be involved in maintaining normal cell adhesion and growth control. That's intriguing, because metastasis requires that cells must first break away from the primary tumor, travel through the bloodstream, and then invade distant organs, where they grow into new tumors. Alterations in TM4 genes might therefore help a tumor cell achieve one or more steps in the metastatic process. Indeed, researchers have evidence suggesting that at least two other proteins in this family have metastasis suppression capabilities in other tumors, including breast and lung cancer and the dangerous skin cancer melanoma.

Consistent with what is known about the other family members, Barrett, Isaacs, and their colleagues have found in a lab assay that prostate cancer cells lacking the *KAI1* protein migrate better than cells with ample amounts of the protein, indicating that the deficient cells are more invasive, a change that may contribute to their increased metastatic ability. "The gene affects the invasive ability of cells," says Isaacs. "It's a relevant phenotype."

But *KAI1*'s ability to stop metastasis may be limited to prostate cancers. Robert Kerbel, a metastasis researcher at Sunnybrook Health Science Center in Toronto, points to the Barrett-Isaacs group's finding that chromosome 11 had no effect on metastasis by rat mammary carcinoma cells. And if the gene's action is specific, that would be intriguing from a biological point of view, Kerbel says, because "there are few, if any, precedents for a tumor-specific suppressor gene." It might mean that cancers take different routes to the metastatic state and that there are other specific metastasis suppressors in the genome. Kerbel adds, however, that more work will be needed to determine whether *KAI1*'s effects are limited to prostate cancer. Barrett and Isaacs agree, and Barrett says the group's plans include experiments in which *KAI1* will be introduced into other kinds of cancer cells to see what effect it has on them.

As that fundamental research proceeds, they are also pushing ahead on the "pragmatic" front that Isaacs says his lab values. They are making antibodies to the *KAI1* protein, which will be employed to measure how much of that protein is in prostate cancers removed from patients. The team can then determine whether patients with decreased levels do worse than those with higher levels, as their theory predicts.

Experience with other cancers suggests, however, that accurate detection of dangerous tumors may require more than one such marker, and there are several other candidates for prostate cancer—including one from another member of the Isaacs family. William Isaacs, John's brother, who is also at Johns Hopkins, and Jack Schalken of Catholic University in Nijmegen, the Netherlands, have evidence indicating that loss of a cell adhesion molecule called cadherin E also correlates with prostate cancer metastasis. In addition, John Isaacs, Barrett, and their colleagues have found that human chromosomes 8, 10, 16, and 17 suppress metastasis by the rat prostatic cancer cells. The team is now trying to identify the genes responsible.

If *KAI1* or these other genes do prove to be markers for metastatic tumors, it "would be a fundamental advance," says pathologist Gary Miller of the University of Colorado Health Sciences Center in Denver, as it would help solve a problem that plagues physicians who care for prostate cancer patients. Better diagnostic techniques—including screening for a protein called prostate surface antigen, whose blood concentration goes up in men with prostate cancer—are identifying increasing numbers of men who have very small islands of tumor cells in their prostate glands. There may be as many as 10 million such men over the age of 50 in the United States alone. But many of those small cancers are likely to be harmless. Autopsy studies have shown, for example, that 50% of men between the ages of 70 and 80 who died of other causes had localized prostate tumors without ever having experienced symptoms.

From these and other findings, urologist Peter Scardino of Baylor College of Medicine in Houston has estimated that 80% of men with small tumors don't need any therapy, while half of the remaining 20% need only surgery to remove their tumors. The remaining 10%, however, will already have microscopic metastases at the time of diagnosis and might benefit from hormonal or other adjuvant therapies. The problem is that with current technology it's not possible to sort out those three groups in the clinic.

Miller is intrigued by the idea that the *KAI1* work could help solve that clinical dilemma. But he cautions that the problem of identifying prostate cancers with metastatic potential may not be solved easily, for host characteristics, such as age, immune status, or nutrition, may also influence whether a metastatic tumor takes root. Kerbel also expresses caution. "Nevertheless," he says, "it seems to be some kind of new suppressor gene, and that makes it very interesting."

–Jean Marx

ASTRONOMY

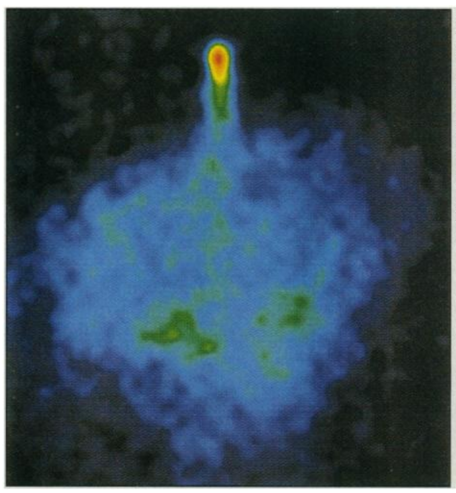
Battle Is Joined Over Gamma Bursts

In 1920, no one knew how the stars shine. No one knew for sure how big our galaxy is, or whether other galaxies existed. These puzzles created deep divisions in the astronomy community, dramatized in April of that year when eminent astronomers Harlow Shapley and Heber Curtis squared off at the National Museum of Natural History to debate some of the most pressing of them.

And while the mysteries that perplex astronomers have changed over the years, the debating tradition has not. In a 75th anniversary celebration* of the Shapley-Curtis debate—held on 22 April in the same auditorium as the 1920 affair—Princeton University's Bohdan Paczyński and Donald Lamb of the University of Chicago took up arms over one of today's knottiest puzzles: How far away are the titanic explosions that about once a day send a burst of gamma rays toward Earth?

Before an audience of 350 astronomers and laypeople, Paczyński and Lamb laid out two radically different answers to that question, answers that entail very different conceptions of what the sources might be. Lamb spoke for the minority of astronomers who think there is strong new evidence that the bursts are coming from our own corner of the

*75th Anniversary Debate: The Distance Scale to Gamma Ray Bursts, 22 April 1995, sponsored by NASA, the Smithsonian Institution, and George Mason University. Principal organizers: Robert Nemiroff and Jerry Bonnell, NASA-Goddard Space Flight Center.



D. FRAIL, N. KASSIM, AND K. WEILER

Blast off. A pulsar (a radio-emitting neutron star) shoots from the wreckage of the supernova explosion in which it was born.

universe, generated by a halo of superdense objects called neutron stars surrounding the Milky Way. Paczyński spoke for the larger camp holding that unidentified gamma ray sources lie much farther away, at "cosmological" distances that stretch to the edge of the observable universe.

One reason that the camps are able to take such different views is that so little is known about the phenomenon. In fact, only one thing is known for sure about the bursts: They are scattered evenly throughout a vast region of space surrounding Earth. Beyond that, each debater was on uncertain ground, and neither conclusively carried the day. The true winner, agree many who attended, was the astronomical community itself.

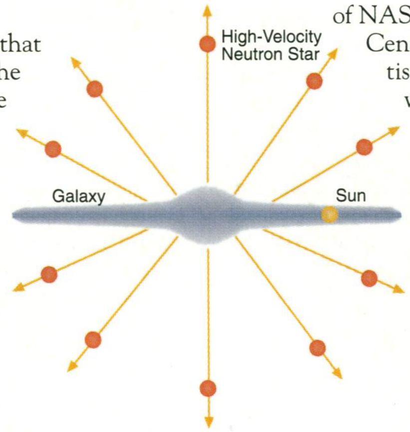
"There has been a strong feeling that this is a settled issue," with the cosmological picture the winner, says Ed Fenimore of Los Alamos National Laboratory. After Lamb's presentation, however, "I think a lot of people see that it is very debatable." As Martin Rees of the University of Cambridge, who moderated the showdown, put it, "Many may go away more confused—though at a higher level than before." By drawing in outside astronomers, the presentation may also have helped sow the seeds of a solution, according to Dale Frail, a radio astronomer at the National Radio Astronomy Observatory in Socorro, New Mexico: "People from other [parts of astronomy] have an enormous amount to contribute. I don't think the gamma ray people will solve it on their own."

Since satellites launched to monitor Soviet nuclear tests detected the first gamma ray bursts in the 1960s, in fact, the mystery has become progressively deeper. Try as they might, astronomers have never been able to identify a known object as the source of a gamma ray burst. And from the beginning, the uniform distribution of bursts has yielded no clues about where their sources might be.

Through the 1970s and 1980s, most specialists speculated that the uniform pattern could be explained if the bursts originated within the Milky Way. In spite of the galaxy's disk shape, objects in the neighborhood of the sun—the brightest stars, for example—look evenly distributed around the night sky. Because the instruments of the time could detect only the brightest gamma ray bursts, it seemed that they too could be right in our neighborhood. A galactic origin also implied a possible power source for gamma ray bursts: neutron stars, collapsed remnants of exploded stars that pepper the galaxy. Neutron stars are so tiny that they are invisible even at close range, but their enormous gravity might be enough to generate a pulse of gamma rays if, say, a chunk of matter fell to their surface and exploded.

If the bursts do come from the galaxy's neutron stars, however, the shape of the galaxy should emerge in the pattern of dimmer bursts, coming from farther away. They should cluster along the galactic plane—the band of sky that harbors the Milky Way. But when detectors sensitive enough to see these faint bursts went into orbit in April 1991 aboard the Compton Gamma Ray Observatory (GRO), they saw nothing of the sort. Just like bright bursts, faint ones are scattered evenly across the sky. It seems that Earth lies at the center of a spherical swarm of gamma ray bursts that isn't confined to the disk of the galaxy.

But how far away is that swarm? For Paczyński, the uniform distribution of the bursts is the clincher. Aided by viewgraphs of how known astronomical objects are placed around the sky, he showed that the only objects with a comparable distribution are in the far reaches of the cosmos. Whatever the gamma ray bursters are, he concluded, they must be out there too. True, theorists have a hard time conceiving of energy sources large enough to generate gamma ray flashes visible at such distances. But Paczyński argued that the logic of the distribution has to take precedence over any theoretical model of a burst source. In any case, he noted, "in astronomy 'large' is not less plausible than 'small.'"



Cloud around the galaxy. A halo of neutron stars flung out by supernovas might be generating gamma ray bursts.

Lamb, however, asked why astronomers should give up neutron stars if there's new evidence that they could do the job after all. True, the neutron stars can't be within the galaxy itself—GRO has ruled that out. But Lamb envisions another possibility: "millions and millions of high-velocity neutron stars streaming out of our galaxy in all directions," forming a vast spherical halo extending for hundreds of thousands of light-years. No one has detected such a halo, but work by radio astronomers over the past year has convinced Lamb and others that it's there. Frail explains that his group and others have spotted young neutron stars shooting out of exploding stars at speeds of 1000 kilometers a second or so—fast enough to escape the gravitational pull of the galaxy. Says Frail, "We gave them [Lamb and his colleagues] the ammunition they needed to fill the halo."

A huge halo of neutron stars can do as good a job at explaining the uniform burst distribution as sources in the distant universe, said Lamb, because it places Earth roughly at the center of a spherical neutron star swarm. And, he argued, the halo hypothesis easily wins out when you consider other clues. With a rhetorical flourish, Lamb presented a series of viewgraphs showing a scale, its two pans representing the dueling hypotheses. He quickly loaded up the galactic side with extra weights: a possible signature of a magnetic field like that of neutron stars in the spectra of some bursts; hints that some bursts repeat, as outbursts from neutron stars are known to do; and resemblances between gamma ray bursts and other gamma flashes known to have come from neutron stars.

Other astronomers, however, note that these items may not be as weighty as Lamb claims. "Each is weak," says Neil Gehrels of NASA's Goddard Space Flight Center, GRO's project scientist. "[Lamb] was putting big weights on that scale, but they really should have been little weights." The hints of repeated gamma ray bursts, for example, showed up in one catalog of events but not in others. Gehrels and many other specialists aren't even convinced a galactic halo can comfortably explain the burst distribution. "The halo model is difficult; it's a stretch," says Gehrels. For a neutron star halo to match the distribution GRO has seen, only those neutron stars that fly out of the galaxy can be allowed to burst—and only after a delay. Jay Norris of NASA Goddard calls those assumptions "tooth fairies."

But Fenimore notes that even if Lamb's picture seems to invoke fairies, "in hindsight a lot of things we now accept as simple looked pretty tooth-fairyish at the time." Moreover, he says, "the cosmology people have their tooth fairies, too," at least when they speculate about what kinds of objects could be broadcasting gamma rays across the width of the universe. All in all, he thinks, "at this point, one shouldn't be taking sides."

Paczyński and Lamb readily admitted they were far from proving their cases. That will require more data, and Paczyński was quick to suggest a strategy: Launch an instrument even more sensitive than GRO to look for a halo of gamma ray bursts around the nearest large galaxy, M31. "If bursts are found in M31," he told Lamb, "I am giving up the cosmological hypothesis." But if not, he added, "I see no way to retain the galactic hypothesis."

Other astronomers have their own ideas about the best way to settle the dispute. Until it's resolved, they will continue to be divided among themselves—and maybe even within themselves, torn between the logic of Paczyński's argument and the richer picture presented by Lamb. As Frail puts it, "My head is in the cosmological camp, but my heart is in the galactic camp."

–Tim Appenzeller