ASTRONOMY

The Link Between Supernovae and Gamma Ray Bursts

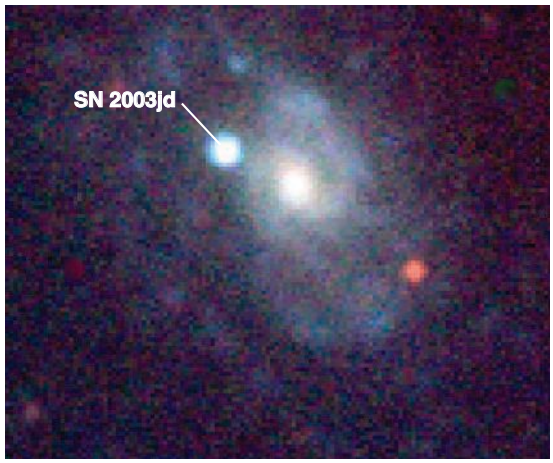
Brian Schmidt

Gamma ray bursts (GRBs) were first discovered in 1967 by American military satellites. The discovery was declassified in 1973; within months, more ideas were published about the origin of these cosmic explosions than there were detected bursts. Since then, observations of thousands of these objects have yielded a deeper understanding of GRBs, but questions remain. For example, it is known that supernovae underlie some GRBs, but how some supernovae produce GRBs remains unclear.

On page 1284 of this issue, Mazzali *et al.* (*1*) shed some light on the link between GRBs and supernovae. They report that supernova 2003jd (see the figure) appears to have been disrupted by a highly asymmetric process, similar to the jets that produce GRBs. Thus, supernova 2003jd may itself be a GRB, with its jets pointed away from Earth when it exploded. This is the first time that researchers have found a supernova that might be a GRB, rather than a GRB that might be a supernova.

The data revolution for GRBs started in 1991 with the launch of NASA's Compton Gamma Ray Observatory. This satellite and its dedicated GRB instrument, BATSE (Burst and Transient Source Experiment), detected more than 8000 bursts until it was sent into the Pacific Ocean in 2000. Before BATSE, models for GRBs ranged from collisions of objects in our solar system to mergers of black holes on the other side of the universe. BATSE observations showed that GRBs are distributed uniformly across the sky, providing strong evidence that they must be occurring in the distant universe (*2*), because it is only at great distances that the sky begins to look uniform.

However, although BATSE was very sensitive to high-energy photons, it could not discern the location of a burst to better than a few degrees uncertainty—an area of sky too large to pinpoint the location of individual explosions. Without a smoking gun, theorists could still bend their models of nearby bursts to fit the observations.



A cosmic explosion 250 million light years away. Observations of supernova (SN) 2003jd show it to be a highly energetic explosion, similar to the hypernovae associated with GRBs. Mazzali *et al.* (*1*) argue that this object was ripped apart by something like a jet, suggesting that SN 2003jd might have been a GRB with its jets directed away from Earth.

In 1996, the Italian-Dutch BeppoSAX satellite was launched. This satellite was not as sensitive as BATSE to gamma rays, but—inspired by predictions that lower-energy x-rays would persist long after the burst of gamma rays—it was able to point an x-ray detector onto a GRB within a few hours of the burst. Beppo-SAX's x-ray detectors could localize these x-ray emissions to much less than 1° uncertainty. This precision was sufficient for optical and radio telescopes to follow up individual objects and look for these explosions.

This strategy paid off when a GRB detected on 28 February 1997 was localized in x-rays; astronomers using the William Herschel Telescope in the Canary Islands then found a fading optical afterglow in a distant galaxy at this location (*3*). This discovery confirmed the cosmological origin of GRBs. Another event detected on 8 May 1997 was determined to be more than 7 billion light years away—halfway across the visible universe (*4*). The huge distance implied an enormous energy. GRBs were thus proclaimed to be the largest bangs in the universe since the big one.

On 25 April 1998, BeppoSAX yielded another surprise. Optical observations of an apparently normal GRB showed a young, very energetic exploding star—a type Ic supernova—at a distance of 80 million light years, one-hundredth the distance of typical GRBs (*5*). The optical brightness of the supernova, named 1998bw, was high for an object at this distance, but its gamma ray, x-ray, optical, and radio brightnesses are several orders of magnitude fainter than for any other GRB observed to date.

Type Ic supernovae are thought to occur when stars 10 to 100 times the mass of the Sun, which have been stripped of their outer layers of hydrogen and helium, run out of nuclear fuel in their center and collapse into neutron stars or black holes. If the dying star that formed supernova 1998bw had lost its outer layers as a result of a merger with another star, it should have been spinning rapidly at the time of its death. Theorists therefore proposed that a jet, produced by the collapse of a rapidly rotating massive star into a black hole, created supernova 1998bw and could produce typical GRBs (*6*). The jet produces observable gamma rays if it points toward the observer; the resulting expanding debris looks like a very energetic type Ic supernova—a so-called hypernova. This model could explain supernova 1998bw, but its relevance to the rest of the GRB population was unclear because of the very different energies of supernova 1998bw and other more distant GRBs.

Since the discovery of 1998bw, much effort has been put into studying the connection between GRBs and hypernovae. The HETE-2 (High Energy Transient Explorer Mission) satellite, launched in 2000, and the Swift Gamma Ray Burst Explorer, launched in 2004, are providing accurate GRB positions for astronomers to chase on an almost daily basis. The light associated with a GRB jet fades quickly, whereas the brightness of a supernova tends to brighten for 1 to 3 weeks. Therefore, 2 weeks past an explosion, a supernova should in most cases outshine a GRB's jet. Observations of nearby GRBs have shown that some objects exhibit supernova-like features as their brightness evolves over time.

The GRB-hypernova connection was confirmed directly on 29 March 2003, when HETE-2 discovered an object one-

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third as distant as any other cosmological GRB to that date. As the object faded, spectra taken with optical telescopes revealed an underlying supernova—an object almost identical to supernova 1998bw (*7*, *8*), but with a gamma ray energy a thousand times higher.

The connection between GRBs and hypernovae thus seems secure, but important questions remain. The GRB jet of supernova 1998bw is much less energetic than that associated with any other GRB to date, and no consensus has emerged as to how a single mechanism could produce supernova 1998bw and the much more powerful bursts in the distant universe.

In addition, the jets of most GRB-hypernovae should aim away from Earth; although not visible in gamma rays, these "misdirected" GRBs should be seen at radio wavelengths (*9*). By comparing the numbers of hypernovae and GRBs in the universe, one can gauge the fraction of hypernovae that are misdirected GRBs. Current data suggest that this fraction should be substantial (*10*). To date, relatively few hypernovae have been discovered in the nearby universe, but none seem to show the intense radio emission expected for misdirected GRBs.

Mazzali *et al.*'s observations of supernova 2003jd, a hypernova at a distance of 250 million light years (see the figure), may resolve the latter problem. The authors provide evidence for the gross asymmetries that are expected for a GRB-hypernova. After the discovery of 2003jd, observers used the Very Large Array radio telescope to look at it, but did not detect it at radio wavelengths. Mazzali *et al.* argue that better radio or x-ray observations are needed to reveal whether this hypernova had a GRB jet. Even if subsequent observations fail to find jets associated with supernova 2003jd, the observations reported in (*1*) provide substantial evidence that the engine that powered supernova 2003jd to become a hypernova is the same that creates GRBs in the distant universe.

With two dedicated GRB telescopes and many programs scanning the sky for supernovae, the next few years promise many more GRB-hypernova connections. These results should help astronomers to further untangle the mysteries of GRBs.

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CELL BIOLOGY

Lessons in Rational Drug Design for Protein Kinases

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How do you design a drug that selectively recognizes one enzyme from among hundreds, all of which share the same substrate? This is the challenge confronting biochemists when developing small-molecule inhibitors of protein kinases, enzymes that regulate cellular growth, homeostasis, and signal transduction. Fifteen years ago, intracellular kinases were considered too ubiquitous to be useful drug targets. But with mounting evidence for highly specific function in many kinases, many pharmaceutical endeavors today have screening programs for inhibitors of this class of enzymes.

Since the mid-1990s, three kinase inhibitors have been approved by the U.S. Food and Drug Administration (FDA) for treatment of chronic myelogenous leukemia, gastrointestinal stromal tumors, and lung tumors (*1*, *2*), and many others are in clinical trials. Each drug works by competitively displacing adenosine 5′-triphosphate (ATP), the nucleotide that binds to the active site of protein kinases. However, because all kinases share molecular recognition determinants in their conserved nucleotide binding pocket, no ATP analog has been found that selectively inhibits a single enzyme. This complicates strategies for developing protein kinase inhibitors. It is difficult to identify small-molecule compounds with high specificity for a single kinase. One must further verify that cellular responses to drug treatment are caused by inhibition of the targeted enzyme.

Enter rational drug design, combining structural determination and computational modeling to identify small molecules that complement amino acid residues within the active site of a target enzyme. So far, only a few successful lead compounds have been developed based on principles of molecular recognition, as opposed to random screening. However, bioinformatics strategies have added new tools to the arsenal, enabling researchers to predict variations in nucleotide and protein sequence that may serve as specificity determinants.

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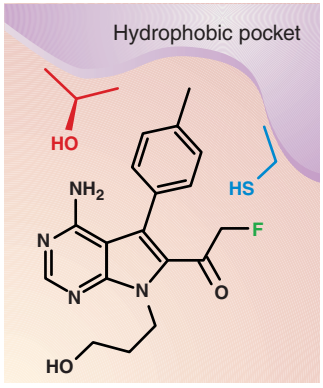
On page 1318 in this issue, Cohen *et al.* (*3*) describe such an approach to designing small-molecule inhibitors of p90 ribosomal S6 kinases (RSKs) by selectively targeting two determinants, or "selectivity filters," in the ATP binding pocket. One selectivity filter, the "gatekeeper," is a residue that flanks a highly variable hydrophobic pocket at the rear of the ATP binding site (*4*). When the side chain of the gatekeeper residue occupies a small volume, the hydrophobic pocket is empty. This allows bulky groups on adenine ring analogs to fit into the pocket. On the other hand, a gatekeeper residue with a large side chain precludes binding of bulky substituents. This mechanistic understanding of selectivity enables candidate inhibitors to be identified by comparing aligned sequences at the gatekeeper position.



Proposed binding mode of a rationally designed inhibitor of p90 RSK. Two "selectivity filters" in the ATP binding site are required for potent inhibition. A threonine residue (red) in the gatekeeper position allows the inhibitor (black) to access a hydrophobic pocket. A poorly conserved cysteine (blue; valine in many kinases) is positioned for attack by the electrophilic fluoromethylketone substituent of the inhibitor (F; green).

The second selectivity filter is a reactive cysteine residue within the active site. The strategy of targeting active-site cysteine residues was previously successful in developing irreversible inhibitors for the epidermal growth factor (EGF) receptor (*5*). However, cysteine residues within active sites of kinases are relatively rare. Using bioinformatics analysis, Cohen *et al.* showed that only 11 kinases among a set of 491 had cysteine residues within the conserved gly-

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