Structural Basis for Broad and Potent Neutralization of HIV-1 by Antibody VRC01

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During HIV-1 infection, antibodies are generated against the region of the viral gp120 envelope glycoprotein that binds CD4, the primary receptor for HIV-1. Among these antibodies, VRC01 achieves broad neutralization of diverse viral strains. We determined the crystal structure of VRC01 in complex with a human immunodeficiency virus HIV-1 gp120 core. VRC01 partially mimics CD4 interaction with gp120. A shift from the CD4-defined orientation, however, focuses VRC01 onto the vulnerable site of initial CD4 attachment, allowing it to overcome the glycan and conformational masking that diminishes the neutralization potency of most CD4-binding-site antibodies. To achieve this recognition, VRC01 contacts gp120 mainly through immunoglobulin V-gene regions substantially altered from their genomic precursors. Partial receptor mimicry and extensive affinity maturation thus facilitate neutralization of HIV-1 by natural human antibodies.

Successful vaccine development often takes advantage of clues from humoral responses elicited by natural infection. For HIV-1, neutralizing antibody responses elicited within the first year or two of infection are generally strain-specific (1) and thus provide limited insight into vaccine design (2). A few monoclonal antibodies from HIV-1–infected individuals, however, are broadly neutralizing, and an effort has been made to facilitate vaccine design by defining their structures (3, 4).

The well-studied broadly neutralizing antibodies to HIV-1—2G12, 2F5, 4E10, and b12—have unusual characteristics that have posed barriers to eliciting similar antibodies in humans (5). Thus, in addition to having broad capacity for neutralization, an appropriate antibody should be present in high enough titers in humans to suggest that it can be elicited in useful concentrations. We and others have screened cohorts of sera from infected individuals to find broadly neutralizing responses that are detectable in a substantial percentage of subjects (6–10). One serum response that satisfies these criteria has been mapped to the site on the HIV-1 gp120 envelope (Env) glycoprotein that binds to the CD4 receptor (8).

Although potentially accessible, the CD4-binding site is protected from humoral recognition through glycan and conformational masking (11). The identification of monoclonal antibodies against this site is described in a companion manuscript (12). In brief, we created resurfaced, conformationally stabilized probes, with antigenic specificity for the initial site of CD4 attachment to gp120 (13). This site, a conformationally invariant subset of the CD4-binding surface, is vulnerable to antibody-mediated neutralization (13), and we used probes specific for this site to identify antibodies that neutralize most viruses (12). In this work, we analyzed the crystal structure for one of these antibodies, VRC01, in complex with
an HIV-1 gp120 core. We deciphered the basis of VRC01 neutralization, identified mechanisms of natural resistance, showed how VRC01 minimizes such resistance, examined potential barriers to elicitation, and defined the role of affinity maturation in gp120 recognition.

Similarities of Env recognition by CD4 and VRC01 antibody. To gain a structural understanding of VRC01 neutralization, we crystalized the antigen-binding fragment (Fab) of VRC01 in complex with an HIV-1 gp120 from the clade A/E recombinant 93TH057 (14, 15). The crystallized gp120 consisted of its inner domain–outer domain core, with truncations in the variable loops V1/V2 and V3 as well as the N- and C-termini, which are regions known to extend away from the main body of the gp120 envelope glycoprotein (16). Diffraction to 2.9 Å resolution was obtained from orthorhombic crystals, which contained four copies of the VRC01-gp120 complex per asymmetric unit, and the structure was solved by means of molecular replacement and refined to a crystallographic R value of 19.7% (Fig. 1 and table S1) (17).

The interaction surface between VRC01 and gp120 encompasses almost 2500 Å², with 1244 Å² contributed by VRC01 and 1249 Å² by gp120 (18). On VRC01, both heavy chain (894 Å²) and light chain (351 Å²) contribute to the contact surface (table S2), with the central focus of binding on the heavy chain–second complementarity-determining region (CDR H2). Over half of the interaction surface of VRC01 (644 Å²) involves CDR H2, a mode of binding that is reminiscent of the interaction between gp120 and the CD4 receptor; CD4 is a member of the V-domain class of the immunoglobulin superfamily (19), and the CDR2-like region of CD4 is a central focus of gp120 binding (Fig. 2A and table S3) (20). For CD4, the CDR2-like region forms antiparallel, intermolecular hydrogen bonds with residues 365gp120 to 368gp120 of the CDR4-binding loop of gp120 (20) (Fig. 2B); with VRC01, one hydrogen bond is observed between the carbonyl oxygen of Gly54VRC01 and the backbone nitrogen of Asp368gp120. This hydrogen bond occurs at the loop tip, an extra residue relative to CD4 is inserted in the strand, and the rest of the potential hydrogen bonds are of poor geometry or distance (Fig. 2C and table S4). Other similarities and differences with CD4 are found: Of the two dominant CD4 residues (Phe43CD4 and Arg59CD4) involved in interaction with gp120, VRC01 mimics the arginine interaction but not the phenylalanine one (Fig. 2, B and C). Lastly, substantial correlation was observed between gp120 residues involved in binding VRC01 and CD4 (fig. S1).

Superposition of the gp120 core in its VRC01-bound form with gp120s in other crystalline lattices and bound by other ligands indicates a CD4-bound conformation [Protein Data Bank (PDB) ID number 3JWD] (16) to be most closely related in structure, with a Cα-root-mean-square deviation of 1.03 Å (table S5). Such superposition of gp120s from CD4- and VRC01-bound conformations brings the N-terminal domain of CD4 and the heavy chain–variable domain of VRC01 into close alignment (Fig. 2), with 73% of the CD4 N-terminal domain volume overlapping with VRC01 (21). This domain overlap is much higher than observed with the heavy chains of other CD4-binding-site antibodies, such as b12, b13, or F105 (table S6). However, when the VRC01 heavy chain is superimposed—on the basis of conserved framework and cysteine residues—on CD4 in the CD4-gp120 complex,
clashes are found between gp120 and the entire top third of the VRC01 variable light chain (Fig. 2D) (22). In its complex with gp120, VRC01 rotates 43° relative to the CD4-defined orientation and translates 6 Å away from the bridging sheet, to a clash-free orientation that mimics many of the interactions of CD4 with gp120, although with considerable variation. Analysis of electrostatics shows that the interaction surfaces of VRC01 and CD4 are both quite basic, although the residue types of contacting amino acids are distinct (fig. S2). Thus, although VRC01 mimics CD4 binding to some extent, considerable differences are observed.

**Structural basis of VRC01 breadth and potency.** When CD4 is placed into an immunoglobulin context by fusing its two N-terminal domains to a dimeric immunoglobulin constant region, it achieves reasonable neutralization. VRC01, however, neutralizes more effectively (Fig. 3A) (12). To understand the structural basis for the exceptional breadth and potency of VRC01, we analyzed its interactive surface with gp120. VRC01 focuses its binding onto the conformationally invariant outer domain, which accounts for 87% of the contact surface area of VRC01 (table S7). The 13% of the contacts made with flexible inner domain and bridging sheet are noncontiguous, and we judged these not to be critical for binding. In contrast, CD4 makes 33% of its contacts with the bridging sheet, and many of these interactions are essential (20). The reduction in inner domain and bridging sheet interactions by VRC01 is accomplished primarily by a 6 Å translation relative to CD4, away from these regions; critical contacts such as made by Phe43CD4 to the nexus of the bridging sheet–outer domain are not found in VRC01, whereas those to the outer domain (such as Arg59CD4) are mimicked by VRC01.

To determine the affinity of VRC01 for gp120 in CD4-bound and non-CD4-bound conformations, we used surface-plasmon resonance spectroscopy to measure the affinity of VRC01 and other gp120-reactive antibodies and ligands to two gp120s: a j4-deletion developed by Harrison and colleagues that is restrained from assuming the CD4-bound conformation (23) or a disulfide-stabilized gp120 core that is largely fixed in the CD4-bound conformation in the absence of CD4 itself (13) (Fig. 3B and fig. S3). VRC01 showed high affinity to both CD4-bound and non-CD4-bound conformations, which is a property shared by the broadly neutralizing b12 antibody (13). In contrast, antibodies F105 and 17b as well as soluble CD4 showed strong preference for either one, but not both, of the conformations.

To assess the binding of VRC01 in the context of the functional viral spike, we examined its ability to neutralize variants of HIV-1 with gp120 changes that affect the ability to assume the CD4-bound state. Two of these mutations, His66AAGp120 and Trp69LeuGp120, are less sensitive (24), whereas as a third, Ser37ThrGp120, is more sensitive to neutralization by CD4 (24, 25). VRC01 neutralized all three of these variant HIV-1 viruses with similar potency (Fig. 3C), suggesting that VRC01 recognizes both CD4-bound and non-CD4-bound conformations of the viral spike. This diversity in recognition allows VRC01 to avoid the conformational masking that hinders most CD4-binding-site ligands (26) and to potentially neutralize HIV-1 (27).

**Precise targeting by VRC01.** Prior analysis of effective and ineffective CD4-binding-site antibodies suggested that precise targeting to the vulnerable site of initial CD4 attachment is required to block viral entry (11, 28). This site represents the outer domain contact for CD4 (13). Analysis of the VRC01 interaction with gp120 shows that it covers 98% of this site (Fig. 4, A and B, and fig. S4), comprising 1089 Å² on the gp120 outer domain, which is about 50% larger than the 730 Å² surface covered by CD4. The VRC01 contact surface outside the target site is largely limited to the conformationally invariant outer domain and avoids regions of conformational flexibility. This concordance of binding is much greater than for ineffective CD4-binding-site antibodies as well as for those that are partially effective, such as antibody b12 (11, 13) (fig. S4).

The outer-domain–contact site for CD4 is shielded by glycan (11, 20). Contacts by the VRC01 light chain (Tyr28VRC01 and Ser36VRC01) are made with the protein-proximal N-acetylglucosamine from the N-linked glycan at residue 813 (23). The outer-domain–contact site of CD4 is shielded by glycan (11, 20). Contacts by the VRC01 light chain (Tyr28VRC01 (23) and Ser36VRC01 (20)) are made with the protein-proximal N-acetylglucosamine from the N-linked glycan at residue 813 (23).
Natural resistance to antibody VRC01. In addition to conformational masking and glycan shielding, HIV-1 resists neutralization by antigenic variation. In a companion manuscript, we show that of the 190 circulating HIV-1 isolates tested for sensitivity to VRC01, 173 were neutralized and 17 were resistant (22). To understand the basis of this natural resistance to VRC01, we analyzed all 17 resistant isolates by threading their sequences onto the gp120 structure (fig. S5). Variation was observed in the V5 region in resistant isolates, and this variation—along with alterations in gp120 loop D—appeared to be the source of most natural resistance to VRC01 (Fig. 4C and figs. S5 and S6).

Because substantial variation exists in V5, structural differences in this region might be expected to result in greater than 10% resistance. The lower observed frequency of resistance suggests that VRC01 employs a recognition mechanism that allows for binding despite V5 variation. Examination of VRC01 interaction with V5 shows that VRC01 recognition of V5 is considerably different from that of CD4 (fig. S7), with Arg61VRC01 in the CDR H2 penetrating into the cavity formed by the V5 and β24 strands of gp120 (fig. S8). The V5 loop fits into the gap between heavy and light chains; thus, by contacting only the more conserved residues at the loop base, VRC01 can tolerate variation in the tip of the V5 loop (Fig. 4D).

Unusual VRC01 features and contribution to recognition. We examined the structure of VRC01 for special features that might be required for its function. A number of unusual features were apparent, including a high degree of affinity maturation, an extra disulfide bond, a site for N-linked glycosylation, a two-amino-acid deletion in the light chain, and an extensively matured binding interface between VRC01 and gp120 (Fig. 5 and fig. S9). We assessed the frequency with which these features were found in HIV-1 Env-reactive antibodies (appendix S1) or in human antibody-antigen complexes (fig. S10 and tables S8 and S9) and measured the effect of genomic reversion of these features on affinity for gp120 and neutralization of virus (Fig. 5, A to D, and table S10).

Higher levels of affinity maturation have been reported for HIV-1-reactive antibodies in general (30) and markedly higher levels for broadly neutralizing ones (31). These maturation levels could be a by-product of the persistent nature of HIV-1 infection and may not represent a functional requirement. Removal of the N-linked glycosylation or the extra disulfide bond, which connects CDR H1 and H3 regions of the heavy chain, had little effect on binding or neutralization (Fig. 5, A and B, and table S10). Insertion of two amino acids to revert the light chain deletion had moderate effects, which were larger for an Ala-Ala insertion (50-fold decrease in binding affinity) versus a Ser-Tyr insertion (fivefold decrease in affinity), which mimics the genomic sequence (Fig. 5C and table S10). Lastly, reversion of the interface was examined with either single-, four-, seven- or 12-mutant reversions. For the single-mutant reversions of the interface to the genomic antibody sequence, all 12 mutations had minor effects [most with a less than twofold effect on the dissociation constant (KD)], with the largest effect for a Gly54Ser change to constant regions indicated. (C) Antigenic variation. The polypeptide backbone of gp120 is colored according to sequence conservation: blue if conservation is high and red if conservation is low. (D) Molecular surface of VRC01 and select interactive loops of gp120. Variation at the tip of the V5 loop is accommodated by a gap between heavy and light chains of VRC01.

276gp120 (29). Thus instead of being occluded by glycan, VRC01 makes use of a glycan for binding. Other potential glycan interactions may occur with different strains of HIV-1 because the VRC01 recognition surface on the gp120-outer domain extends further than that of the functionally constrained CD4 interaction surface, especially into the loop D and the often-glycosylated V5 region (fig. S5).

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having a $K_d$ of 20.2 nM] (table S10). Larger effects were observed with multiple (four, seven, or 12) changes (Fig. 5D and table S10). Thus, although VRC01 has a number of unusual features, no single alteration to genomic sequence substantially altered binding or neutralization.

Elicitation of VRC01-like antibodies. The probability for elicitation of a particular antibody is a function of each of the three major steps in B cell maturation: (i) recombination to produce nascent antibody heavy and light chains from genomic V_{H}/D-J and V_{C}_{H}, J precursors, (ii) deletion of auto-reactive antibodies, and (iii) maturation through hypermutation of the variable domains to enhance antigen affinity. For the recombination step, a lack of substantial CDR L3 and H3 contribution to the VRC01-gp120 interface (table S2) indicates that specific V_{C}_{H}, J or V_{K}(D)J recombination is not required (32) (fig. S11). The majority of recognition occurs with elements encoded in single genomic elements or cassettes, suggesting that specific joining events between them are not required. Within the V_{H} cassette, a number of residues associated with the IGHV1-02*02 precursor of VRC01 interact with gp120; many of these are conserved in related genomic V_{H}b8, some of which are of similar genetic distance from VRC01 (fig. S12). These results suggest that appropriate genomic precursors for VRC01 are likely to occur at a reasonable frequency in the human antibody repertoire.

Recombination produces nascent B cell–presented antibodies that have reactivities against both self and nonself antigens. Those with auto-reactivity are removed through clonal deletion. With many of the broadly neutralizing antibodies to HIV-1, such as 2G12 (glycan reactive) (33, 34), 2F5, and 4E10 (membrane reactive) (35, 36), this appears to be a major barrier to elicitation. Although this remains to be characterized for genomic revertants and maturation intermediates, no auto-reactivity has so far been observed with VRC01.

The third step influencing the elicitation of VRC01-like antibodies is affinity maturation, which is a process that involves the hypermutation of variable domains combined with affinity-based selection that occurs during B cell maturation in germinal centers (37). In the case of VRC01, 41 residue alterations were observed from the genomic V_{H} gene and 25 alterations from the V_{C}_{H} gene (including a deletion of two residues) (fig. S13) (38). To investigate the effect of affinity maturation on HIV-1 gp120 recognition, we reverted the V_{H} and V_{C} regions of VRC01, either individually or together, to the sequences of their genomic precursors. We tested the affinity and neutralization of these reverted antibodies (Fig. 6A) and combined these data with the genomic reversion data obtained while querying the unusual molecular features of VRC01 (previous section) (Fig. 6B).

No antibodies containing V_{H} and V_{C} regions, which were fully reverted to their genomic precursors, bound gp120 or neutralized virus (39). Binding affinity and neutralization showed significant correlations with the number of affinity-matured residues ($P < 0.0001$). Binding to stabilized gp120 did not correlate well with other types of gp120 or to neutralization (table S11), which is related in part to greater retention of binding to VRC01 variants with genomically reverted V_{C} regions. Extrapolation of the correlation to the putative genomic V gene sequences predicted binding affinities of 0.7 ± 0.4 μM $K_d$ for gp120 stabilized in the CD4-bound conformation and substantially weaker affinities for nonstabilized gp120s (Fig. 6B and fig. S14).

No single affinity maturation alteration appeared to affect affinity by more than tenfold, suggesting that affinity maturation occurs in multiple small steps, which collectively enable tight binding.

**Fig. 5.** Unusual VRC01 features. The structure of VRC01 displays a number of unusual features, which if essential for recognition might inhibit the elicitation of VRC01-like antibodies. (A to D) Unusual features of VRC01 are shown structurally (far left), in terms of frequency as a histogram with other antibodies (second from left), and in the context of affinity and neutralization measurements after mutational alteration (second from right and right). Affinity measurements were made by means of enzyme-linked immunosorbent assay to the gp120 construct used in crystallization (93TH057), and neutralization measurements were made with a clade A HIV-1 strain Q842.d12. Additional binding and neutralization experiments are reported in table S10. (A) N-linked glycosylation. The conserved tri-mannose core is shown with observed electron density, along with frequency and effect of removal on affinity and neutralization. (B) Extra disulfide. Variable heavy domains naturally have two Cys, linked by a disulfide; VRC01 has an extra disulfide linking CDR H1 and H3 regions. This occurs rarely in antibodies, but its removal through mutation to Ser/Ala has little effect on affinity or neutralization. (C) CDR L1 deletion. A two-amino-acid deletion in the CDR L1 prevents potential clashes with loop D of gp120. Such deletions are rarely observed; reversion to the longer loop may have a moderate effect on gp120 affinity. (D) Somatically altered contact surface. (Left) The VRC01 light chain is shown in violet, and the heavy chain is in green. Residues altered by affinity maturation are depicted with “balls,” and contacts with HIV-1 gp120 are colored red. Approximately half of the contacts are altered during the maturation process. Analysis of human antibody-protein complexes in PDB shows this degree of contact surface alteration is rare; reversion of each of the contact sites to the genome sequence has little effect (table S10), although in aggregate the effect on affinity is larger.
to HIV-1 gp120. When the effects of VRC01 affinity maturation reversion events are mapped to the structure of the VRC01-gp120 complex, they are broadly distributed throughout the VRC01 variable domains rather than focused on the VRC01-gp120 interface. Noncontact residues therefore appear to influence the interface with gp120 through indirect protein-folding effects. Thus, for VRC01 the process of affinity maturation entails incremental changes of the nascent genomic precursors to obtain high-affinity interaction with the HIV-1 Env surface.

**Receptor mimicry and affinity maturation.**

The possibility that antibodies use conserved sites of receptor recognition to neutralize viruses effectively has been pursued for several decades. The recessed canyon on rhinovirus that recognizes the unpaired terminal immunoglobulin domains of intercellular adhesion molecule–1 highlights the role that a narrow canyon entrance may play in such occlusion of bivalent antibody-combining regions (40), although framework recognition can in some instances permit entry (41). Partial solutions such as those presented by antibody b12 (neutralization of ~40% of circulating isolates) (12, 13) or by antibody HJ16 (neutralization of ~30% of circulating isolates) (42), a recently identified CD4-binding-site antibody, may allow recognition of some HIV-1 isolates.

With VRC01, the potency and breadth of neutralization (over 90%) suggest a more general solution. It remains to be seen how difficult it will be to guide the elicitation of VRC01-like antibodies from genomic rearrangement, through affinity maturation, to broad and potent neutralization of HIV-1. Accumulating evidence suggests that the VRC01-defined mode of recognition is used by other antibodies (12). These findings suggest that VRC01 is not an isolated example and probably provides a template for a general mode of recognition. The structure-function insights of VRC01 described here thus provide a foundation for rational vaccine design that is based not only on the particular mode of antibody-antigen interaction but also on defined relationships between genomic antibody precursors, somatic hypermutation, and interface-recognition elements.

**References and Notes**

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17. The four independent copies of the VRC01-gp120 complex in the asymmetric unit resembled each other closely for the antibody variable domain–gp120 components, with an Cα-root-mean-square deviation of less than 0.2 Å. Elbow variation, however, between variable and constant domains was apparent, and we found one copy (molecule 1) to be more ordered than the others. In the figures, we display molecule 1; see fig. S15 for a comparison of all of the molecules in the asymmetric unit.
18. Surface areas of interaction reported in this paper were determined with the program PISA, as implemented in CCP4 (44). Values were about 20% higher than those reported previously for the gp120-C4D complex (20), which were obtained using the program MS (45).
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27. In a companion paper (32), we show that VRC01 binding induces 17β and CCR5 binding in the context of monomeric gp120 with an unusual entropy signature characteristic of transiting to the CD4-bound state (46); neutralization data, however, show that VRC01 does not induce 17β or CCR5 binding in the context of the viral spike. This difference probably arises from the more constrained gp120 conformation in the trimeric spike. Thus, although VRC01 is able to induce large conformational changes in monomeric HIV-1 gp120 that resemble those induced by CD4, VRC01 interaction with gp120 does not depend on these conformational changes.
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32. Four residues are provided by the CDR H3, Asp99KARE to Trp100B, with a combined interaction surface of 123 Å² (tables S3 and S12). These four residues are probably contributed by the Ω segment (IGHD3-16Ω2), and none of them appears critical to VRC01 recognition because changes are observed in two of these residues in the closely related
broadly neutralizing antibody VRC03, which was one of two antibodies we isolated along with VRC01 (2). Meanwhile, three residues are provided by the CDR L3—Arg97, Glu69, and Phe97—whose combination surface of 190 Å² (tables S3 and S13). These three residues lie at the junction between V and J genes. They make important hydrophobic interactions with loop D of gp120, and two of them are conserved between VRC01 and VRC03. Although it is difficult to know how precisely the CDR L3 needs to be aligned, with only three contact residues variation at the V, j gene junction should provide sufficient diversity for it to be represented in the repertoire.

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38. Analysis of the HIV-1 Env-reactive antibody repertoire from infected individuals shows increased levels of affinity maturation (6). Analysis of a subset of this data (appendix S3) containing 147 heavy and 147 light chains from HIV-1 Env-reactive antibodies reveals an average of 15 alterations (30 maxima) for the heavy chain and an average of 8.6 alterations (22 maximum) for the light chain (fig. S13). In terms of the subset of HIV-1 Env-reactive antibodies that are broadly neutralizing (such as 2G12, 2F5, 4E10, and b12), antibodies b12 and 2G2G have 45 and 51 changes, respectively, relative to nearest genomic precursors in their V and J segments of the heavy chain (31).
39. Similar significant reductions in affinity have been observed with reversion of other broadly neutralizing antibodies to HIV-1 to putative genomic sequences (47–49); these observations have led to the suggestion that the dramatically reduced germine affinity for gp120 might hinder the initiation of affinity maturation of these antibodies (50). That is, if the affinity for gp120 of the genomic precursor of a broadly neutralizing antibody were below the threshold required for the nascent B cell to mature, then maturation would either not occur or would need to occur in response to a different immunogen. This lack of guided initiation of the maturation process may provide an explanation for the absence of such broadly neutralizing antibodies in the first few years of infection. Conversely, the introduction of modified gp120s with affinity to genomic precursors and affinity maturation intermediates could provide a mechanism by which to elicit antibodies like VRC01.

Novae are thermonuclear explosions on a white dwarf surface fueled by mass accreted from a companion star. Current physical models posit that shocked expanding gas from the nova shell can produce x-ray emission, but emission at higher energies has not been widely expected. Here, we report the Fermi Large Area Telescope detection of variable γ-ray emission concurrent with the nova outburst from V407 Cyg. We propose that the material of the nova shell, by which to elicit antibodies like VRC01.

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Novae are thermonuclear explosions on a white dwarf surface fueled by mass accreted from a companion star. Current physical models posit that shocked expanding gas from the nova shell can produce x-ray emission, but emission at higher energies has not been widely expected. Here, we report the Fermi Large Area Telescope detection of variable γ-ray emission (0.1 to 10 billion electron volts) from the recently detected optical nova of the symbiotic star V407 Cygni. We propose that the material of the nova shell interacts with the dense ambient medium of the red giant primary and that particles can be accelerated effectively to produce n° decay γ-rays from proton-proton interactions. Emission involving inverse Compton scattering of the red giant radiation is also considered and is not ruled out.

V 407 Cygni (V407 Cyg) is a binary system consisting of a Mira-type pulsating red giant (RG) with a white dwarf (WD) companion; these properties place it among the class of symbiotic binaries (1). Though one of the more active symbiotic systems, V407 Cyg has historically shown an optical spectrum in quiescence dominated by the Mira-like RG (M6 III) and only weak emission lines [see, for example, (2)]. Its infrared continuum (consistent with a dusty wind) and maser emission (3) are detected at levels similar to other symbiotic Miras [for instance, R Aqr (4)]. One outstanding anomaly of V407 Cyg is a strong Li I λ6707 line indicative of an overabundance of Li relative to normal Mira RGs (5, 6). Based on the 745-day pulsation period of the RG (7) and the Mira period-luminosity relation (8), we adopt the distance D = 2.7 kpc, estimated as the mean derived from photometry in three near-infrared bands, assuming an extinction E(B-V) = 0.57 (2).

A nova outburst from V407 Cyg was detected on 10 March 2010 (9); it had a magnitude of ~6.9 in an unfiltered charge-coupled device image obtained at 19:08 UT. Subsequent densely sampled observations show that the outburst was followed by a smooth decay, though the precise epoch of the nova is formally uncertain by up to 3 days, due to the time gap from the pre-outburst image (Fig. 1). Monitoring of the source over the past 2 years indicates pre-outburst magnitude values in the range of 9 to 12 [see the supporting online material (SOM)]. V407 Cyg has been monitored optically for decades and has shown earlier signs of optical brightening on month-long time scales by one to two magnitudes in the B and V bands (around 1936 and 1998) from typical V-band magnitudes of 13 to 16 (2, 10, 11), but the magnitude of the recent nova was unprecedented.

Here, we report on a high-energy γ-ray source (Fig. 2) positionally coincident with V407 Cyg detected after the nova (12) during routine automated processing of all-sky monitoring data from the Fermi Large Area Telescope (LAT) (13). A γ-ray light curve (1-day time bins) of this source generated from an analysis of all LAT data reveals that the first significant detection (4.3σ) was, in fact, on 10 March, indicating that the γ-ray activity began on the same day as the reported optical maximum of V407 Cyg (Fig. 1; see also SOM). The observed 10 March flux is up to a factor of 3 larger than the 1-day upper limits (unless otherwise noted, 95% confidence limits are reported throughout) on the pre-outburst days. To further isolate the onset of detectable γ-ray emission, we divided the 10 March data into 6-hour intervals,

Supporting Online Material
www.sciencemag.org/cgi/content/full/science.1192819/DC1
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References
Appendix S1
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