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Viral enzymes
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Viral genomes show unequalled diversity, ranging from single-stranded DNA to double-stranded RNA. Moreover, viruses can quickly adapt to the host’s immune response and drug treatment. Although they tend to make optimal use of the host cell’s reservoir of proteins, viruses need to carry some enzymatic functions with them, as they may not be available or accessible in the infected cell. Recently, progress has been made in our structural understanding of viral enzymes involved in all stages of the viral life cycle, which includes entry, hijack, replication and exit stages.

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Introduction
The prime characteristic of viruses is their absolute dependence on a host for reproduction and, as such, they are obligate parasites and a plague to all living organisms. Back in 1898, the Dutch scientist Beyerinck and the German researchers Loeffler and Frosch established that, based on filtration experiments, the causative agents of certain (plant and animal) diseases were clearly smaller than all known bacteria. Only two years later, yellow fever was the first human viral disease to be recognized (Major Reed and assistants, US Army, Havana, 1900) and, to date, more than 1938 virus species belonging to 287 genera of 73 families have been identified [1]. Probably, viruses are as old as life on Earth, but a broad public awareness is only emerging now, in view of the current AIDS pandemic and the recent outbreaks of severe acute respiratory syndrome (SARS) and bird flu.

Compared to cells, viruses are indeed small, with (apparently) minimized genomes that mostly encode proteins not provided by the host cell. Not only do viruses try to make optimal use of the host’s accessible reservoir of enzymes, but also they can quickly and efficiently adapt to any changes in the host, its immune response and drug treatment. Finally, because of their genomic flexibility, many viruses, in particular RNA viruses, are able to change their host range and cross species barriers. In contrast to living organisms, viral genomes show a breath-taking diversity, from single-stranded (ss) DNA to double-stranded (ds) RNA, with a size of up to 400 kb (e.g. Phycodnaviridae). An intriguing exception is the Acanthamoeba polyphaga mimivirus (APMV), which features a genome size of 1.2 mb. The genetic information is often programmed in a highly efficient way, displaying features such as overlapping genes and making full use of the possibility to encode both homo- and hetero-oligomers as the biologically active species. In principle, a small, naked, infectious DNA or RNA strand of a few thousand bases that can somehow enter a living cell, be replicated and translated by cellular enzymes, and finally leave the cell to infect new ones would suffice to qualify as a virus, that is, an obligate parasite in need of the host’s energy-supplying and protein-synthesizing capabilities. Nevertheless, viruses generally bear an exterior coating (capsid or envelope) and have a variety of enzymes and auxiliary proteins, many of which are not available or accessible (due to compartmentalization) in the infected cell.

With the recent increase in public awareness, research into viral proteins has benefited from increased funding (e.g. the VIZIER project, www.vizier-europe.org, and the SEPSDA project on the SARS coronavirus, www.sepsda.info). As a result, a flood of structural information is becoming available that will help propel the discovery of antiviral lead compounds by structure-based drug design or virtual screening. In this review, current structural studies of viral enzymes are summarized and discussed.

We will discuss these studies within the framework of a viral life cycle composed of entry, hijack (taking control and dodging defense), replication (transcription and translation) and, finally, exit stages. Viral proteins are usually divided into structural and non-structural types; although most enzymes are classified as non-structural, some structural proteins may display enzymatic activity as well. Viral enzymes involved in the entry or exit steps will be discussed in one section.

Entry and exit: crossing cell barriers
Although some plant viruses make it into their target cells through open wounds, most viruses bind to a receptor molecule at the cell surface and then have to cross the cell
membrane. Receptor binding is not an enzymatic process and therefore is not discussed here, but often the same viral glycoprotein that binds to cellular receptors through one domain (or fragment) catalyzes membrane fusion through another domain. The latter activity exhibited by these structural proteins can be considered 'enzymatic' (see [2] for a more detailed review). A few structures of such fusion cores described in the past two years will be mentioned here; these include relevant fragments of the SARS coronavirus (CoV) spike (S) protein (see [3] for a review), human parainfluenza virus 5 F protein [4], Semliki Forest virus glycoprotein E1 [5], Dengue virus envelope (E) protein ([6]; see also [7]) and glycoprotein B of herpes simplex virus 1 [8]. Upon pH shift and/or proteolytic cleavage, these proteins undergo conformational change, thereby exposing a hydrophobic fusion peptide that can insert into the host cell membrane.

For efficient egress of newly formed virions from the host cell, receptor molecules located at the surface of infected cells have to be modified or degraded. Influenza neuraminidase, a sialidase, cleaves sialic acid moieties from receptor molecules, thereby preventing the rebinding of viruses to the surface of the same, already infected, host cell. Very recently, the X-ray structure of avian influenza virus neuraminidase (a type-I neuraminidase) has been determined, revealing an extra cavity adjacent to the active site that closes upon ligand binding ([9*]; PDB codes 2HTY, 2HU0 and 2HU4; the last two structures contain the drug oseltamivir). This cavity is not observed in the N2 and N9 (type-II) variants of the enzyme that were used for the structure-based design of oseltamivir (Tamiflu) and zanamivir (Relenza). Thus, this finding opens new avenues for the design of neuraminidase inhibitors.

**Hijacking: engaging host defense and acquiring cell control**

Once the virus is inside the host cell, it needs to take control of the cell and evade host defense strategies while initiating, in a timely manner, replication and translation processes. Viral offensive measures affect a wide variety of host defensive strategies, for example, modification of signaling pathways and cellular machines. Interferons play a key role in cell defense and viruses counteract accordingly. Recognition of viral nucleic acids through pattern-recognition receptors (e.g. Toll-like receptor 3 and cytosolic RNA helicase RIG-I; reviewed in [10]) is the first step in the induction of the innate immune system. But the viruses strike back: the NS3-NS4A serine protease of hepatitis C virus (HCV) cleaves Cardif, an adaptor molecule involved in the recognition of viral dsRNA by retinoic acid inducible gene-1 (RIG-I; [11*]), thereby blocking interferon-β production. The simian virus 5 V protein hijacks DNA damage binding protein 1 (of the DDB1–Cul4A ubiquitin ligase complex) by inserting an entire helix into a pocket formed by two domains of the three-β-propeller DDB1 structure ([12**]; PDB code 2B5L), inducing degradation of STATs (signal transducer and activator of transcription) and thereby obstructing interferon signaling. Furthermore, the interferon-inducible and dsRNA-stimulated protein kinase PKR, a key player in the innate response to viral infection, is targeted by many DNA and RNA viruses (reviewed in [13]); for example, the human cytomegalovirus (HCMV) TRS1 gene product [14] seems to sequester PKR in the nucleus, away from both its activator, cytoplasmic dsRNA, and its substrate, eukaryotic initiation factor 2α (eIF2α). As a consequence, phosphorylation of eIF2α and the subsequent shutdown of protein synthesis are prevented.

Besides crippling or evading host defense, viruses need to slow down host mRNA translation to promote viral mRNAs. This is often achieved by modification of eukaryotic initiation factors (eIFs) or the poly(A)-binding protein (PABP). Like picornavirus and calcivirus proteases (see [15]), HIV-1 and -2 proteases efficiently cleave PABP [16]. The 2A cysteine proteinase of coxackievirus 4B ([17]; see below) cleaves eukaryotic initiation factor eIF4G, thereby blocking host mRNA translation. Once host mRNA translation and host defense are perturbed, viral transcription and translation can proceed promptly. Viruses ensure that cap-independent eukaryotic initiation of viral (subgenomic) mRNA translation can proceed normally by employing specific viral proteins and/or internal ribosome entry sites (IRES) to recruit ribosomes. Instead of a 7-methylguanosine (m7G) cap structure at the 5’ end, (sub)genomic RNAs are, in several cases, covalently linked to viral protein VPg (viral protein genome-linked, see next section), which appears to substitute for the 5’-terminal m7G cap moiety in ribosome recruitment. Using GST-based pull-down assays, VPg was shown to interact with several eIFs and ribosomal protein S6 in norovirus-infected cells [18]. The 3’-untranslated region of turnip yellow mosaic virus (TYMV) harbors a tRNA-like structure (TLS) that acts as a molecular Trojan horse and is responsible for the internal initiation of polyprotein synthesis [19].

**Replication: nucleic acid and protein synthesis**

DNA and RNA viruses alike encode at least one protein involved in nucleic acid synthesis: whereas all RNA viruses have an RNA-dependent polymerase, some DNA virus genomes merely encode a helicase (e.g. paroviruses and polyomaviruses) or primase (e.g. herpes simplex virus), and yet others encode a complete machinery for DNA replication (e.g. poxviruses). For translation, by contrast, they all depend on host cell ribosomes and translation factors. It would require a major effort to encode (large parts of) a translational machine: in bacteria, more than 150 different macromolecules (RNA and protein) are directly involved in protein biosynthesis, with nearly 60 of them organized in the ribosome. Located in
the cytosol, the host cell translational apparatus is freely accessible to all types of viruses and there is no need for them to carry translation factors with them. This is in contrast to nucleic acid synthesis, for which many of the relevant host enzymes are contained in the nucleus. Mimivirus is a remarkable exception to this rule; this virus carries a substantial portion of the translational apparatus with it [20].

Viral enzymes are notoriously difficult to handle and crystallize, as many of them are part of larger assemblies; in a pure and concentrated state, the single, isolated proteins often tend to aggregate. Nevertheless, more and more three-dimensional structures are being determined and viral enzymes such as polymerases, helicases and especially proteases prove amenable to crystallization.

There are two main classes of viral RNA-dependent RNA polymerases (RdRps, reviewed in [21]), primer dependent and primer independent (de novo). The picornavirus and calicivirus RdRps represent one class; they display a more accessible active site cavity, enabling them to accommodate the small VPg protein that acts as a primer in RNA synthesis. The foot-and-mouth disease virus (FMDV) VPg protein lines the RNA-binding cleft and primer independent (de novo) RdRps contain additional structural elements that fill most of the active site cavity (see [21]), thereby enabling de novo RNA synthesis using a single NTP as a primer (see also [26**]).

The RdRps are a major target for the development of antiviral compounds. In the ‘thumb’ domain of NS5B, the RdRp of HCV, the binding sites for thiophene-based non-nucleoside inhibitors (NNIs) ([27]; PDB codes 2D3U, 2D3Z and 2D41) and allosteric GTP (see [28*]) are in close proximity. Apparently, this part of the ‘thumb’ domain, located approximately 35 Å away from the polymerase active site (the ‘palm’ domain), fulfills an important regulatory function that can be modulated by GTP or NNI binding. The dimeric structure of HCV NS5 domain I (a large phosphoprotein and active component of the HCV replicase) reveals a groove with an exposed Trp84 residue ([29]; PDB code 1ZH1); the groove is large enough to accommodate an RNA helix. An N-terminal amphipathic α-helix places NS5A on the membrane, which is essential for the assembly of a functional viral replication complex [30,31]. The polyadenylate polymerase heterodimer of vaccinia virus is made up of a catalytic component, polyadenylate polymerase VP55, and a capping mRNP (mRNA: nucleoside-2’-O-)-methyltransferase, processivity factor VP39 ([32*]; PDB code 2GA9); polyadenylation of mRNAs in poxviruses is crucial for virion maturation. Recently, the structures of the DNA polymerases of HCMV and herpes simplex virus have been reported [33,34].

Since the global outbreak of SARS in 2003, much effort has been invested to elucidate the structures of components of the SARS-CoV replicase complex. However, the structure of the RdRp (also called non-structural protein 12, Nsp12) itself has remained elusive so far, due to difficulties with producing the full-length protein in sufficient quantities and crystallizing it. The crystal structure of the hexadecameric (8:8) complex between Nsp7 and Nsp8 has been determined recently ([35**]; PDB code 2AHM). The complex features a central channel of ~30 Å diameter (Figure 2), sufficiently wide to accommodate dsRNA. Together with the positive electrostatic potential of the inner walls of the channel, this suggests that Nsp7–Nsp8 may function as a processivity factor for the RdRp, reminiscent of the β2-clamp of bacterial DNA polymerases. This is a nice example of successful functional assignment of an Nsp of unknown function resulting from the structural proteomics projects dealing with SARS-CoV; previously, the function of Nsp9 as an ssRNA-binding protein had been correctly deduced from its crystal structure ([36,37]; PDB codes 1QZ8 and 1UW7). A new homodimeric form has recently been found for Nsp9 from human coronavirus 229E (R. Ponssamy et al., unpublished). Nsp10 is another coronaviral protein without known function, but it was recently demonstrated that it has two zinc fingers and binds dsRNA [38–40]. Upon dsRNA binding, the Nsp10 dodecamers observed in one crystal form ([39]; PDB codes 2G9T and 2GAd) apparently dissociate into monomers [38], as observed in the other crystal form ([40]; PDB code 2FYG).

Several viruses encode a macrodomain (viral X-domain), as found in proteins associated with histones or involved in chromatin metabolism. Initially, a subdomain of Nsp3 of SARS-CoV was proposed to possess ADP-ribose 1’-phosphate phosphohydrolase (ADRP) activity ([41]; PDB code 2ACF). Very recently, the ADRP domain of Nsp3 was shown to bind efficiently to poly(ADP-ribose) in vitro, both in its free state and when bound to poly(ADP-ribose) polymerase 1 ([42*]; PDB code 2FAY) (Figure 3a). Its phosphohydrolase activity was redefined as being poor and the true biological function of this protein in the viral life cycle remains to be elucidated. The
membrane-bound replicase complex of the coronaviruses harbors an endonuclease, NendoU (Nsp15), a manganese-dependent enzyme specific for uridylate. The crystal structure of Nsp15 revealed that it possesses a novel fold and an active site that appears to characterize a separate endonuclease family ([43][C15], [44][C15]; PDB codes 2H85 and 2GTH) (Figure 3b). The biologically active unit of this enzyme is a dimer of trimers with six independent active sites.

The structure of the coronavirus helicase remains to be determined, but recently structures became available for the helicases of other RNA viruses. A comparison of the NS3 HCV helicase [45] and both the yellow fever virus (YFV) ([46][C15]; PDB code 1YMF) (Figure 4) and Dengue virus ([47]; PDB code 2BMF) helicase structures revealed that only the C-terminal domains (third domain) are quite unrelated between the flaviviruses and HCV. The lack of nucleotide specificity nicely correlates with the observation that the adenine and ribose moieties of a bound ADP, in the YFV helicase–nucleotide complex [46][C15], protrude into solution. An arginine is expected to be critical for conformational switching upon NTP hydrolysis, although the mode of action is not well understood. One implication of modeling work seems to be that a 3’ single-stranded tail of about nine nucleotides would be required for the initiation of the unwinding reaction [47]. An interesting set of structural ‘snapshots’ has now become

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Figure 1

Comparison of polymerase-bound protein and RNA primers. VPg–UMP, overview in (a) and details in (c), is observed in the crystal structure ([22][C15]; PDB code 2F8E) in a position remarkably similar to that of the template–primer RNA duplex, overview in (b) and details in (d) ([23]; PDB code 1WNE). Except for Tyr3, only the mainchain atoms of VPg are shown for clarity: carbon atoms of VPg are colored blue and those of UMP cyan. Magnesium and manganese ions are shown as dotted balls in (a and c) and the template–primer RNA duplex is in stick form in (b and d). As a point of reference, three amino acids (of conserved elements in the active site) are shown as stick models: D245, Y336 and D338.
fairly complete for the helicase E1 protein subunit of papillomavirus [48**]. An E1 monomer possesses two DNA-binding elements, a loop and a helix, that bind opposing DNA strands. Two E1 homodimers are initially loaded onto the DNA [49], each of which is further expanded to produce a hexamer that surrounds a single DNA strand [48**]: one strand of DNA passes through the hexamer channel, sliding along the DNA-binding loops that sequentially track the oligonucleotide backbone.

A few viral proteins have been shown to contain disulfide bonds, even though they fold in the reducing environment of the eukaryotic host cytoplasm. Enzymes involved in disulfide bond isomerization, and perhaps others that catalyze peptidyl-prolyl cis/trans isomerization, may therefore play a role in viral infectivity. This has been underscored by structural and functional investigations of vaccinia virus G4 disulfide oxidoreductase, an enzyme that displays a thioredoxin fold with the usual Cys-X-X-Cys motif [50].

Viral proteases are essential for processing virally encoded polyproteins during replication, in co- and post-translational steps. Because of their importance for viral replication, assembly and infectivity, they are potential targets of antiviral drugs. It seems that the proteases of at least some RNA viruses could qualify as targets of inhibitors with the desirable relatively broad specificity, due to similarities in their overall architecture and in their substrate-binding sites. The crystal structure of a birnavirus protease (VP4 of blotched snakehead virus) visualized, for the first time, a serine–lysine catalytic dyad in the viral world ([51*]; PDB code 2GEF). The amino group of the lysine residue is almost completely buried and therefore probably deprotonated. Bacterial proteases using a similar active site include LexA and the Lon protease, although the latter enzyme oligomerizes and requires ATP hydrolysis for proteolytic activity. Named after the 3C domain of the picornavirus polyprotein, a large number of proteases from RNA viruses have a chymotrypsin-like fold, but
most of them have a cysteine rather than a serine residue as the nucleophile. Two crystal structures of closely related norovirus 3C-like proteases revealed that the active site features a catalytic Cys–His–Glu triad ([52,53]; PDB codes 1WQS and 2FYQ). The cysteine can be replaced by serine, suggesting that the enzyme works through a general base mechanism involving a non-charged Cys–His pair rather than a thiolate–imidazolium ion pair (as has been shown to exist in papain-like proteinases).

The picornavirus genome comprises a single-stranded, messenger-oriented RNA molecule of 7.5 kb that is used as the template for both replication and translation. Processing of the single polyprotein encoded by this genome is initiated by the 2A proteinase (2Apro), which cleaves the bond between the structural protein VP1 and its own N terminus, and is subsequently completed by the 3C proteinase (3Cpro) or its 3CD precursor. In addition to polyprotein processing, 2Apro of coxsackievirus B3 is involved in cleaving dystrophin, leading to acquired dilated cardiomyopathy, and in interrupting host protein synthesis by cleaving eukaryotic initiation factors eIF4GI and eIF4GII, as well as the PABP. An NMR structure has been published of 2Apro of coxsackievirus B4, revealing the expected chymotrypsin-like architecture, with a proper Cys–His–Asp catalytic triad ([17]; PDB code 1Z8R). Such a triad has also been seen in the 3C proteinases of FMDV ([54]; PDB code 2BHG) and tobacco etch virus ([55,56]; PDB codes 1Q31 and 1LVN). This is significant, because earlier structures of picornavirus 3C proteinases revealed irregularities with regard to the acidic partner of the catalytic triad; either the aspartate residue was found oriented away from the active site histidine, such as in hepatitis A virus 3Cpro ([57]; PDB code 1QA7), or it was replaced by glutamate, such as in poliovirus 3Cpro [58], in human rhinovirus 3Cpro ([59]; PDB code 1CQQ) or in the recently determined structure of 3C proteinase of coxsackievirus 3B (K Anand et al., unpublished).

All of the viral proteases mentioned thus far more or less prefer glutamine over glutamate residues at the P1 position of the substrate, although this distinction is not so clear in case of the enzyme from FMDV. However, the chymotrypsin-like serine protease from Sesbania mosaic virus (SeMV), an ssRNA plant sobemovirus, is specific for glutamate at P1. The activity of this enzyme is modulated by the binding of VPg, whose Trp43 residue is believed to interact with an exposed aromatic patch near the C terminus of the SeMV proteinase ([60*,61*]; PDB code 1ZYW). Thus, at least three different functions have been described for VPg-like peptides in viral replication: it can substitute for the 5’-terminal m7G cap moiety in binding to initiation factors and in ribosome recruitment; it can act as a primer in viral RNA synthesis; and it can increase the activity of certain viral proteases. Another chymotrypsin-like viral protease whose catalytic activity is augmented...
by a peptide cofactor is the NS3-NS4A protease of HCV ([62]; PDB code 1A1R). This enzyme continues to be the target of numerous efforts in drug design (e.g. [63]).

In addition to the chymotrypsin-like β-barrel domains I and II, the coronavirus main proteinases (M\textsuperscript{pro}, also called 3C-like proteinases, 3CL\textsuperscript{pro}) have a C-terminal helical domain that is involved in dimerization of the enzyme [64–66]. The catalytic center consists of a Cys–His dyad; the position of the third member of a proper triad is taken by a highly conserved water molecule that is involved in multiple hydrogen-bonding interactions. Another unique feature not present in the 3C proteases is that the N terminus of one M\textsuperscript{pro} monomer is involved in shaping the substrate-binding site of the other; therefore, dimerization is essential for catalytic activity [64–66]. Among this protease family, SARS-CoV M\textsuperscript{pro} is now by far the best investigated because of its paramount importance as a target for the treatment of SARS [67,68]. A pH-dependent switch has been proposed to be responsible for the activation of this enzyme; at low pH, at least one monomer of the homodimeric enzyme tends to be in a catalytically incompetent conformation, with the oxyanion hole and the S1 pocket collapsed [66,69], whereas both monomers appear to be active at higher pH [66,70]. The transition between the two conformations is believed to depend on the protonation/deprotonation of a histidine residue (His163) that interacts with the P1 glutamine residue of the substrate; this has been reproduced using molecular dynamics simulations [69]. Several structures of complexes with peptidomimetic inhibitors have been determined for the enzyme [66,71*,72,73] and compounds that acylate the active site cysteine residue were also described as potent inhibitors [74,75]. Peptidyl aldehydes have been designed and synthesized as potentially reversible inhibitors [76]. In silico screening efforts have resulted in the identification of a few non-covalent binders that act as competitive inhibitors [77].

The M\textsuperscript{pro} performs 11 of the 14 cleavage reactions necessary to process coronaviral polyproteins and to generate the components of the replicase machinery. The remaining three cleavage sites in the N-proximal portion of the polyproteins are substrates of viral papain-like proteinases (PL\textsuperscript{pro}). Most coronaviruses have two of these enzymes (PL1\textsuperscript{pro} and PL2\textsuperscript{pro}), but the SARS virus genome only encodes the latter. Most interestingly, it has been found that this protease not only cleaves the polyproteins after LXGG sequences, but also has a deubiquitinating function [78–80]. The crystal structure of SARS-CoV PL\textsuperscript{pro} ([81*]; PDB code 2FE8) revealed that the enzyme comprises four distinct domains (Figure 5), three of which form an extended right-handed architecture in which they have been nicknamed ‘thumb, palm and finger’, although they are different from the corresponding features of DNA polymerases. The N-terminal 62 residues form a distinct ubiquitin-like domain. The active site comprises a catalytic Cys–His–Asp triad, the cysteine of which is contributed by the thumb domain and the two other residues by the palm domain. The tip of the finger domain carries a structural zinc ion that is ligated by four cysteine sidechains. The closest structural relatives of SARS-CoV PL\textsuperscript{pro} are the cellular deubiquitinating enzymes HAUSP (herpes-associated ubiquitin-specific protease) and USP14 (ubiquitin-specific protease 14). In addition to ubiquitin, SARS-CoV PL\textsuperscript{pro} also removes ISG15 from target proteins. ISG15 is a ubiquitin-like molecule induced by interferon α/β as part of the innate immune response against viral infections [82]. Apparently, SARS-CoV protects itself from interferon-triggered
innate immune response by interfering with ISG15 or ubiquitin conjugation pathways. But what is the role of the N-terminal ubiquitin-like domain carried by PLpro itself? Ratia et al. [81**] have entertained the interesting idea that it may serve as a decoy to detract cellular ubiquitinating enzymes from modifying proteins of SARS-CoV.

Finally, several viruses encode glycosyltransferases that are involved in the post-translational modification of the structural proteins. Paramecium bursaria Chlorella virus (PBCV) is probably the first virus known to encode enzymes involved in sugar metabolism: the N-terminal domain of PBCV GDP-d-mannose 4,6 dehydratase adopts a modified Rossmann fold, displaying a seven-stranded parallel β-sheet with a 3-2-1-4-5-6-7 topology, and the smaller C-terminal domain is probably involved in nucleotide-sugar substrate binding [83]. The Sulfolobus turretedicosahedral virus (STIV) glycosyltransferase [84] possesses the glycosyltransferase superfamily A fold (GT-A), displaying both the canonical DXD motif and a putative catalytic base.

Conclusions
Structural virology has made significant progress over the past few years. The outbreak of SARS in 2003 has triggered increased research activity in the field, including a few structural proteomics projects. Viral enzymes are promising targets for antiviral drug discovery and such drugs are in great need in view of the dramatic increase in the number of viral outbreaks in recent years. It has to be realized that, in the case of an outbreak, it will take at least six months and probably twelve until a vaccine will be ready for use; hence, we will have to resort to drugs that have been discovered and preclinically developed before the outbreak. Of course, such drugs should exhibit broad antiviral activity and, even though real broad-band antivirals may remain an illusion (as opposed to the existing broad-band antibacterials), preliminary results with inhibitors of RNA virus proteases suggest that there may be at least groups of viruses susceptible to one and the same drug. Structural results on viral target enzymes are of course essential to design inhibitors or discover them by in silico screening, and it is indeed satisfying that threedimensional structures of viral enzymes are determined with increasing pace.

A nice side effect of the structural biology of viral proteins, especially complexes thereof, is that a lot can also be learnt about the cellular machines or pathways that are targeted by viruses (e.g. see [11**]). Also, it is increasingly realized that molecular mimicry seems to be used by viral components, for example, the small Vpg proteins that are able to reprogram or redirect large molecular machines. The large diversity and dynamics of viral genomes seem to be reflected in the three-dimensional structures of viral proteins and their complexes.

Update
Very recently, Imbert et al. [85] have shown that Nsp8 (and its complex with Nsp7) may in fact constitute a second RdRp in SARS-CoV.

Acknowledgements
The authors acknowledge support by the European Commission through VIZIER (Comparative Structural Genomics of Viral Enzymes Involved in Replication; contract LSHG-CT-2004-511960) and SEPSDA (Sino-European Project on SARS Diagnostics and Antivirals; contract SP22-CT-2004-003831). RH thanks the Innovation Fund of the Government of Schleswig-Holstein and the Fonds der Chemischen Industrie for continuous support. Figures were prepared with the PyMol molecular graphics system (DeLano Scientific LLC, South San Francisco, CA, USA).

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