Developments in Basic Science Research

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A large percentage of the topics covered at the 10th Conference on Retroviruses and Opportunistic Infections in Boston were concerned with basic research aspects of HIV-1 and AIDS. Topics that generated particular interest included the identification of host factors that restrict retrovirus and lentivirus infection. In addition, a number of presentations concerned the use of RNA interference (RNAi) as a tool for understanding HIV biology, and several presentations discussed approaches to therapeutic exploitation of RNAi in HIV/AIDS.

Host Restriction Factors for Lentivirus Infection

In the past year, there has been significant progress in the identification of cellular mechanisms that impact the susceptibility of the host cell to retrovirus and lentivirus infection. This progress has included the identification of the cellular target for the HIV-1 Vif protein (Sheehy et al, *Nature,* 2002). In a plenary lecture (Abstract 5), Malim presented research on a protein called CEM-15, which is the cellular target for Vif. Research from the laboratories of Kabat and Malim had proposed that primate cells contain an inhibitor that blocks HIV-1 infection and that the Vif protein combats this cellular factor in order to allow primate cells to support viral infection. These initial studies provided the impetus for research aimed at identifying the inhibitory factor. Using a subtractive hybridization approach, Malim and colleagues identified a number of complementary DNA segments (cDNAs) that were unique to cells in which Vif was required for viral infection. After genetic and virologic characterization, one of these cDNAs, CEM-15, exhibited the predicted properties of the cellular inhibitor. For example, CEM-15 was expressed only in cells in which Vif was required for viral infection. In the presence of CEM-15, HIV-1 virions exhibited a normal morphology and composition yet were noninfectious. CEM-15 exhibits homology with a cellular protein called apobec 3G, which belongs to a small family of RNA editing proteins. Since some of these apobec proteins have cytidine deaminase activity, this homology suggests a model in which CEM-15 may edit viral RNA by deaminating cytidines to uridine to the extent that reverse transcription is stalled when genomic viral RNA modified by CEM-15 is used as a substrate.

In an extension of these studies, Landau and colleagues (Abstract 72) have been studying the influence of the murine CEM-15 homologue on viral replication. It was demonstrated that murine CEM-15 can potently inhibit HIV-1 infectivity to a greater extent than can human CEM-15. Although studies with HIV-1 have suggested the Vif defect acts at late steps in viral reverse transcription, in the presence of murine CEM-15, initiation of reverse transcription was blocked. There also appeared to be some differences in the sites of action for human CEM-15 and murine CEM-15. In human cells, HIV-1 Vif must be present in virus-producing cells in order to combat the action of CEM-15. However, murine CEM-15 could inhibit HIV-1 replication when expressed in target cells. Importantly, the inhibitory action of murine CEM-15 could not be impaired by HIV-1 or simian immunodeficiency virus (SIV) Vif. This finding suggests that CEM-15 possesses 2 functional domains, 1 that regulates its inhibitory activity on viral replication and 1 that is targeted by Vif. Takaori-Kondo and colleagues (Abstract 202) also suggested that the RNA editing activity of CEM-15 is required for its ability to suppress viral infectivity. Thus, a point mutant of CEM-15 that lacked RNA editing activity was unable to suppress the infectivity of a Vif-defective virus. It was also demonstrated that the subcellular localization of CEM-15 was not affected by Vif. Therefore, the mechanism through which Vif blocks the CEM-15 effect on viral infectivity remains undetermined. Taken together, these studies highlight the potential importance of Vif/CEM-15 interaction as a therapeutic target. In order to adapt to its new host, HIV-1 has evolved a Vif protein that, by an as-yet-uncharacterized mechanism, inactivates CEM-15. This relationship provides the rationale for therapeutic strategies that prevent CEM-15 inactivation by Vif either using small molecules that prevent their interaction or compounds that mimic the action of CEM-15.

Bieniasz (Abstract 111) discussed resistance factors other than CEM-15 that influence susceptibility of the cell to virus replication. For example, an inhibitory activity referred to as Ref 1, which acts at the level of gag to block an early step in viral infection, has been identified (Towers et al, *Proc Natl Acad Sci U S A,* 2000; Besnier et al, *Proc Natl Acad Sci U S A,* 2002). This inhibitory activity is manifest by certain monkey cell lines that are resistant to HIV-1 infection. This resistance factor is saturable in that infection can proceed at very high multiplicities of infection. Although the identity of the cellular resistance factor is unknown, it appears to target the gag protein, since virus-like particles minimally containing gag and protease are able to saturate the restriction factor. The step in the viral replication cycle that is inhibited by Ref 1 awaits identification but may be manifest at the uncoating step. Identification of the restriction factor should aid the development of therapeutic strategies that exploit these innate host restriction factors of lentivirus infection.

Accessory Proteins

Nef

A number of studies related to the biological activities of Nef were featured at the conference (Abstracts 203-211). One of the models proposed for the

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mechanism of action of Nef in enhancement of viral replication relates to the impact of the protein on host-cell activation status. Since virus replication is optimal in activated CD4+, a number of studies have suggested that HIV-1 Nef may enhance the activation state of the host cell. However, this model requires that Nef be expressed in cells that are refractory to productive infection. Studies from Wu and Marsh (*Science,* 2001) suggested that Nef may be expressed from unintegrated DNA, and presumably, this early expression of Nef augments host-cell activation status so as to promote completion of subsequent events in the viral life cycle. In an extension of this theme, Gillim and Klotman (Abstract 208) suggested that Nef expressed from unintegrated DNA is also able to effect down-regulation of CD4+. As alluded to above, numerous studies have focused on the possibility that Nef augments host-cell activation state to improve conditions for viral replication. Choi and colleagues (Abstract 207) presented evidence that the impact of Nef on viral replication depends on the stimulus with which CD4+ cells are induced to proliferate. When CD4+ T cells were incubated with human umbilical-vein–derived monolayers and treated with interferon γ, the T cells proliferated. The replication of wild-type virus in CD4+ T cells stimulated in this way was approximately 50-fold higher than replication for Nef-deleted virus. This study provides intriguing evidence that lymphocytes induced to proliferate by physiologic signals may be the preferred environment in which Nef enhances viral replication.

Previous studies have shown Nef to be incorporated into virions (Pandori et al, *J Virol,* 1996). Forshey and Aiken (Abstract 205) presented a study indicating that Nef remains associated with the viral reverse transcription complex following the fusion and uncoating steps. The authors proposed that this may allow Nef to influence viral infectivity at the reverse transcription step; it is also possible, however, that Nef that is introduced by incoming virions may influence the activation state of the host cell to promote conditions for viral infection. In addition, Nef has a well-documented ability to down-regulate CD4+ receptor expression on the cell surface. Lama and Argañaraz (Abstract 203) presented evidence that the relative abilities of different Nef alleles to down-regulate CD4+ strongly impact viral replication in cells with high levels of CD4+ expression and in primary lymphocytes. Furthermore, Nef alleles isolated from HIV-1-infected individuals at varying stages of disease exhibited differential impact on CD4+ receptor expression, and HIV-1 variants containing Nef alleles that more efficiently down-regulated CD4+ consequently replicated more efficiently in primary lymphocytes. Collectively, these findings suggest that CD4+ down-regulation may be an important determinant for HIV-1 pathogenesis. In a related study (Abstract 204), Lundquist and colleagues presented evidence that the impact of Nef on CD4+ down-regulation is context-dependent, in that deletion of Nef more profoundly impacted the infectivity of X4-tropic HIV-1 than of R5-tropic viruses. The authors proposed that the specific requirement for Nef in X4-tropic virus replication is a consequence of the more efficient envelope-mediated down-regulation of CD4+ by those viruses.

HIV-1 has been shown to bud selectively from lipid rafts. In addition, the composition of lipid rafts may impact the composition of virions and ultimately virion infectivity. Heaton and colleagues (Abstract 206) presented evidence that Nef is targeted to lipid rafts and that this targeting is important for the ability of Nef to down-regulate major histocompatibility complex (MHC) class 1 but less so for its ability to down-regulate CD4+. Further, increased replication capacity and pathogenicity of wild-type virus relative to virus with the *nef* gene deleted (ΔNef) has been demonstrated in a number of model systems, including SIV-infected macaques, the SCID-Hu PBL model of HIV-1 infection, and human thymic organ cultures. Agostin and Su (Abstract 209) demonstrated that the ability of Nef to effect thymocyte depletion in thymic organ cultures required neither the CD4+ or MHC class 1 down-regulating activities of Nef nor interaction of Nef with cellular kinases PAK1/2, RAF-1, or ASK-1, or the vacuolar adenosine triphosphatase V1H. Thus, a novel motif in Nef may involve its ability to direct thymocyte depletion.

Vpr

A number of studies (Abstracts 213-219) were concerned with various aspects of Vpr activity, particularly the contribution of Vpr to HIV-1 cytopathogenicity. Cytopathic effects of HIV-1 and CD4+ T lymphocytes are manifest both by syncytial structures and by single-cell killing, and the envelope glycoprotein is a critical determinant in both processes. However, it is becoming increasingly apparent that Vpr may also play a role in virus-mediated cell killing through the induction of apoptotic cell death. Bolton and Lenardo (Abstract 217) also presented evidence that virion-associated Vpr and expressed Vpr induce cell death by a nonapoptotic mechanism. Vpr-mediated cell death required the C-terminus of Vpr, in that viruses containing C-terminal Vpr deletions did not exhibit the characteristic cytopathic properties of wild-type virus. In a variation on this theme, induction of cell death by Vpr was found to occur by a DNA damage-signaling pathway (Abstract 213). The serine-threonine kinase ATR becomes activated in response to DNA damage. Expression of a dominant-negative ATR or disruption of ATR by RNA interference blocked the ability of Vpr to induce cell-cycle arrest. Thus, in addition to its possible role in Vpr-mediated cell death, the DNA damage-signaling pathway may also play a role in Vpr-mediated cell-cycle arrest.

Another study (Abstract 217) presented evidence that expression of viral transcripts from unintegrated viral DNA requires Vpr. When the levels of HIV-1 transcripts were compared for wild-type and integrase-defective viruses, expression was higher for virions containing an intact Vpr. The ability of Vpr to impact expression from unintegrated DNA was unrelated to the cell-cycle arrest activity of Vpr and was independent of Tat. Although it would be important to determine whether Vpr can influence the expression of unintegrated DNA that contains a functional integrase, this study may shed light on the mechanism through which unintegrated DNA serves as a template for the expression of viral proteins.

Vpu

Vpu genes are contained within the genomes of HIV-1 and SIV_{CPZ}; however, HIV-2 and other SIV lineages may contain a Vpu-like activity within the envelope glycoprotein, at least with regard to CD4+ down-regulation. Courgnaud and colleagues (Abstract 73) identified a novel SIV lineage with a Vpu gene (SIV_{MON}). This lineage was identified in a seroprevalence survey of wild-born monkeys in Cameroon and supports the hypothesis that the SIV_{CPZ} lineage is a recombinant of related SIV lineages. Vpu is a small transmembrane protein, although the impact of membrane localization on Vpu activity is not well-understood. Singh and colleagues (Abstract 212) compared the subcellular localization of Vpu proteins from HIV-1 subtype B and C isolates. Subtype B Vpu was localized within the endoplasmic reticulum/Golgi complex, but subtype C Vpu was localized at the cell surface, and the cytoplasmic domain was responsible for this membrane localization. Thus, although the Vpu proteins from subtype C and subtype B viruses may localize to different cellular compartments, it remains to be determined whether the biologic activities of Vpu from these subtypes exhibit different biologic properties.

Aspects of Virus Replication

Preintegration Events

Arguably, one of the least well-understood events in virus replication is the uncoating of the viral capsid and release of viral nucleic acids into the cytoplasm. Aiken and colleagues (Abstract 17) presented evidence that the fusogenic activity of HIV-1 envelope glycoprotein is coordinated with HIV-1 core maturation. Immature HIV-1 particles were unable to fuse efficiently with T cells, but truncation of the gp41 cytoplasmic tail or cleavage of the gag precursor Pr55 gag between the MA and NC domains rescued fusion. This finding suggests that HIV-1 fusion is coupled to core maturation through binding of the gp41 cytoplasmic domain to Pr55 gag. This study provides new targets for the development of strategies that interrupt HIV-1 entry and uncoating.

Virus entry requires colocalization of receptors and coreceptors at the point of virus contact. Steffens and Hope (Abstract 20) provided evidence that receptor and coreceptor molecules colocalize in the region of lipid rafts to facilitate the interactions that lead up to HIV-1 fusion. The study also found that receptor and coreceptor molecules were linked with actin-containing structures. This finding may reconcile independent observations on the role of the cytoskeleton and lipid rafts in increasing the efficiency of virus entry.

Several studies were concerned with analyzing the impact of receptor and coreceptor density and location on virion infectivity, susceptibility to entry inhibitors, and resistance to antibody-mediated neutralization. Although transmembrane envelope glycoproteins of lentiviruses contain long cytoplasmic tails, passage of SIV_{mac} in human cell lines selects for variants with truncated cytoplasmic tails. One study (Abstract 19) demonstrated that truncation of the cytoplasmic domain of gp41 dramatically increased envelope content on virions by 25- to 50-fold. Although the increased envelope content led to a modest increase in viral infectivity, it was accompanied by a dramatic reduction in sensitivity to neutralizing antibody. Thus, truncation of the gp41 cytoplasmic tail by in vitro passage favors emergence of variants with increased infectivity in vitro, but evolutionary pressure for long cytoplasmic domains in vivo favors increased neutralization resistance. In a related study (Abstract 23), Reeves and colleagues found that the density of coreceptor molecules on target cells influenced virus susceptibility to entry inhibitors such as enfuvirtide (T-20) and TAK-779. There was an inverse correlation between coreceptor expression levels and sensitivity to enfuvirtide. In addition, there was an inverse correlation between gp120/coreceptor affinity and sensitivity to entry inhibitors, presumably because the more rapid fusion kinetics conferred by greater envelope/coreceptor affinity reduces the time during which enfuvirtide is able to interact with the viral envelope.

A large number of coreceptor molecules for HIV-1 and SIV infection have been identified, but there is little definitive information that coreceptors other than CCR5 and CXCR4 are directly involved in HIV-1 replication and pathogenesis in vivo. Willey and colleagues (Abstract 273) presented evidence for an unidentified receptor for the chemokine vMIP-1 that may serve as a functional coreceptor for a number of HIV-1 and SIV variants. A subset of HIV-1, HIV-2, and SIVs were found to infect primary endothelial cells and astrocytes that lack CCR5 and CXCR4 expression by a CD4+-dependent mechanism that was resistant to inhibitors of CXCR4- and CCR5-dependent infection. This finding suggests the presence of an alternative functional coreceptor on these cells, which about 25% of the dual tropic HIV-1 strains tested were able to utilize. In addition, this coreceptor was active on primary peripheral blood mononuclear cells (PBMCs). The ability to block use of this coreceptor using vMIP-1 suggests that a vMIP-1 receptor was involved. Although CCR8, CXCR6, and GPR1 all bind vMIP-1, the expression of these receptors did not correlate with usage of the alternative coreceptor. Collectively, this suggests the presence of an alternative coreceptor, which is expressed on primary cells and which may be functionally involved in viral tropism in vivo.

Several studies have suggested that R5 viruses are selectively transmitted. This result has been interpreted as suggesting that cells such as macrophages, where infection is CCR5-dependent, may be early reservoirs for the establishment of infection following viral transmission. In order to gain further insight into the mechanism of R5 dominance, Harouse and colleagues (Abstract 125lb) compared the transmissibility of pathogenic SIV-HIV hybrid viruses (SHIVs) that exhibit X4 or R5 tropism. Both X4- and R5-specific SHIVs were detectable in the plasma of coinfected animals within the first 3 weeks of infection, but between 3 and 6 weeks, coincident with the onset of antiviral immunity, R5 viruses predominated. When transmission was compared in coinfected animals in which CD8+ cells had been depleted, X4 viruses predominated. This finding suggests that R5 viruses predominate after transmission because they are

less susceptible to inhibition by CD8+ suppressor cells. One interpretation of this result is that the infected macrophage reservoir may be less susceptible to cytotoxic T lymphocyte surveillance. An important question is whether a similar mechanism may explain the switch from R5 to X4 viruses that occurs in approximately 50% of patients during progression to late-stage disease.

It is now becoming apparent that DC-SIGN may be one of several attachment factors expressed on dendritic cells that mediate virus transmission to CD4+ T cells. KewalRamani (Abstract 110) presented evidence that the role of DC-SIGN in virus transmission is context-dependent and restricted in some cell types. A variety of cell lines expressing low levels of DC-SIGN were examined for ability to transmit HIV-1. Although all cell lines were able to bind HIV-1 at similar efficiencies, some cells did not efficiently transmit the virus. Therefore, there may be additional cellular factors that function collaboratively with DC-SIGN in virus transmission. Bobardt and colleagues (Abstract 270) presented evidence to suggest that cell-surface proteoglycans such as syndecans may capture HIV-1 on the surface of endothelium and serve as transreceptors for HIV-1 infection of T cells. By analogy, DC-SIGN expressed on dendritic cells has been suggested to act as a transreceptor involved in virion capture and transmission to neighboring T cells. Although the syndecans were able to serve as an attachment factor for a broad range of lentiviruses, the syndecans could not substitute for primary or coreceptors in virus entry. The authors proposed that the endothelium, via expression of syndecans, may trap virions and subsequently transmit virions to T cells when the T cells come into close contact with the capillary endothelium.

McDonald and colleagues (Abstract 113) presented evidence for a mechanism that promotes polarization of viral particles on dendritic cells at the point of contact with T cells. Using fluorescent microscopy visualization of HIV-1 particles incorporating green fluorescent protein, the investigators demonstrated that HIV-1 was recruited to sites of cell contact between monocyte-derived dendritic cells and T cells. The mechanism through which virions were localized to the dendritic-cell/T-cell contact point is unclear but likely represents an efficient mechanism through which captured virions are positioned to increase the likelihood of contacting a substrate T cell. This study raises some important questions for future research, such as whether it is possible that HIV-1 may have evolved the ability to exploit this mechanism by specifically activating the localization by, for example, polarization of the cytoskeletal network. In addition, as T cells are activated following contact with infected dendritic cells, it would be interesting to determine whether, in addition to virions, costimulatory molecules involved in T-cell stimulation are also polarized at the point of contact between the dendritic cell surface and the T cell.

It has been suggested that signals generated through receptor/coreceptor molecules enhance post-entry events in the viral replication cycle. Matthews and colleagues (Abstract 292) presented evidence that R5 HIV-1 binding to CCR5 elicits a signal that allows infection of resting cells. The authors also attempted to identify signaling intermediaries that are involved in this process. Treatment of resting memory T cells with either MIP-1β (CCR5 ligand) or R5 HIV-1 led to activation of the protein tyrosine kinase Pyk2. Replication of R5 HIV-1 in resting memory T cells was hindered by inhibitors of the signaling molecules PI3 kinase or c-Src kinase but not by G_α inhibitors. Thus, signals generated by R5 HIV-1 binding to CCR5 may involve PI3 kinase and c-Src kinase, which enhance conditions for subsequent steps in virus replication. It will be interesting to determine the fate of infected resting memory T cells and whether these cells are able to enter a latent state of infection.

Integration

A long-standing question in retrovirus biology regards whether there are selective sites for viral integration. Two studies presented opposing viewpoints regarding the selective integration of retroviruses into genes. In one study using a nonlentivirus system, Maxfield and colleagues (Abstract 69) examined retroviral integration into a highly inducible endogenous gene under induced and uninduced transcriptional states. When the frequencies of integration events downstream of the inducible gene were compared under induced and uninduced conditions, there were fewer integration events into the gene when actively transcribing. The authors proposed that active genes may be less desirable integration substrates because of the steric hindrance imposed by RNA polymerase II. Alternatively, double-stranded DNA may be a preferred substrate for the preintegration complex, or remodeling of chromatin by transcription may generate a less desirable substrate for integration. In the second study (Abstract 70), Mitchell and colleagues took a different approach to study lentivirus integration sites in primary T cells. The group had previously established that following infection of a T-cell line, HIV-1 integrates selectively within genes. In an extension of that study, the investigators looked at integration sites in primary lymphocytes and again concluded that genes were favored substrates for integration. It will be important to determine whether, in primary lymphocytes, the genes selected for integration are also transcriptionally active.

Emiliani and colleagues (Abstract 74lb) described the identification of a novel cellular factor that binds HIV-1 integrase. The protein, LEDGF/p75, is a chromatin-associated transcriptional coregulator that is involved in cell survival and the stress response. Inhibition of LEDGF/p75 expression by RNA interference resulted in impairment of HIV-1 infection. Although the studies are preliminary, they suggest that LEDGF/p75 may be a functional cofactor for HIV-1 integration and a potential target for therapeutic intervention.

Late Events

The last few years have seen significant advances in understanding of virus assembly and, in particular, viral and cellular determinants of the budding process. Retroviral and lentiviral gag proteins contain late domains that bind distinct cellular cofactors that promote virus budding. Several groups have identified TSG101, a component of the

vacuolar protein-sorting machinery, as required for the budding of viruses such as HIV-1 and Ebola (Garrus et al, *Cell,* 2001; VerPlank et al, *Proc Natl Acad Sci U S A,* 2001; Martin-Serrano et al, *Nat Med,* 2001). In an extension of these studies, Martin-Serrano and colleagues (Abstract 24) presented evidence that VPS28, a component of the TSG101-containing ESCRT-I complex, interacts with TSG101 and that the interaction is required for particle budding, as was TSG101 multimerization. In addition, a minimal TSG101 domain that contained multimerizing activity exhibited dominant-negative inhibitory activity on HIV-1 budding.

While significant strides are being made in the identification of cellular cofactors for virus budding, Wild and colleagues (Abstract 14) described a novel small-molecule inhibitor of HIV-1 budding. PA-457, a derivative of betulinic acid, exhibited 50% inhibitory concentration (IC_{50}) in the low nanomolar range. PA-457 appeared to interfere with gag processing and specifically with cleavage of p25 to p24. PA-457 did not affect HIV-1 protease activity and was active against nonnucleoside reverse transcriptase inhibitor-resistant and protease inhibitor-resistant viruses. Although the molecular basis of HIV-1 inhibition by PA-457 awaits identification, it may represent a potential new class of antiretrovirals.

As alluded to earlier, several studies have suggested that HIV-1 buds selectively from lipid rafts. When lipid rafts are disrupted in virus-producing cells, the resulting viral particles have a lower infectivity, although the point at which infectivity is impaired is unclear. Cavrois and colleagues (Abstract 18) presented evidence that HIV-1 fusion to target cells is markedly impaired when lipid rafts are disrupted in virus-producing cells. In addition, although Nef has been suggested to localize to lipid rafts, the enhancement of viral infectivity by Nef was independent of budding from lipid rafts. This finding suggests that the composition of proteins within the virion that is dictated by the site of virus budding does not impact enhancement of viral infectivity by Nef.

RNA Interference

RNA interference (RNAi) is a process by which 21- to 23-nucleotide RNAs act as guides to target homologous messenger RNAs (mRNAs) for degradation. First identified in plants, RNAi has been documented in a variety of species, including worms, flies, yeast, and mammals. In the worm, RNAi is initiated when double-stranded RNA is processed by the enzyme Dicer into discreet 21- to 23-nucleotide fragments. These processed interfering RNAs are incorporated into a multiprotein complex and then guide the complex to mRNAs to which the interfering RNAs are homologous. Proteins within this complex subsequently degrade target mRNAs. Because long, double-stranded RNA triggers a type 1 interferon response, initiating RNAi from long, double-stranded RNA is problematic in mammalian cells. However, synthetic 21- to 23-nucleotide double-stranded RNAs, also referred to as small interfering RNAs (siRNAs), bypass the requirement for Dicer and initiate the degradation of mRNAs bearing homologous sequences without activating interferon responses (Zamore, *Nat Struct Biol,* 2001). With this approach, it is possible to target almost any RNA for degradation. Since HIV-1 employs an RNA intermediate in its replication cycle, the virus represents a rather obvious target for manipulation by RNAi.

In the past year, several studies demonstrated the utility of siRNAs for inhibiting HIV-1 infection in vitro (Pomeranz, *Nature Med,* 2002). A number of studies (see presentations in sessions 10 and 37) described progress in the use of RNAi to modulate viral replication, to modulate expression of cellular cofactors for viral replication, and to adapt vector strategies for delivery of interfering RNAs to cells both in vitro and in vivo. The majority of studies described the in vitro activity of siRNAs against a variety of viral genes such as *tat/rev* (Abstract 52), Vif (Abstract 220), and cellular cofactors such as the coreceptors CXCR4 and CCR5 (Abstracts 221, 222, 223, 226, and 231A), as well as the primary receptor CD4+ (Abstract 227). Several studies demonstrated the inhibition of HIV-1 replication by siRNAs in primary cells including lymphocytes and macrophages (Abstracts 51, 220, and 225). In an exciting study, Lieberman (Abstract 51) demonstrated in vivo utility of siRNAs using a murine model of autoimmune hepatitis. The fas siRNAs injected intravenously were able to protect mice from fas-induced acute liver damage and death, suggesting that siRNAs are capable of direct uptake into hepatocytes. This finding has clear implications for potential treatment of pathogenic states involving the liver. Several studies (Abstracts 50, 226, 227, 228, and 229) also detailed progress in the development of viral vectors that express siRNAs under constitutive and inducible promoters.

Although the therapeutic applicability of RNAi to HIV/AIDS remains an open question, it nevertheless is an important tool with which to study HIV-1 biology. In particular, the ability of RNAi to inhibit the expression of cellular genes provides an opportunity to validate cellular factors that may play a role in virus replication and to prioritize those factors that are functionally involved in this process.

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Additional Suggested Reading

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