remains, as is the case for all antiretroviral agents. Beyond strand transfer inhibitors, momentum has been growing in the field collectively known as non-catalytic site integrase inhibitors (NCINIs). These NCINIs are believed to be allosteric inhibitors of the integrase enzyme that disrupt the interaction of IN with the key cellular co-factor, lens epithelium-derived growth factor (LEDGF/p75). The proposed role for this interaction is to guide the preintegration complex to transcriptionally active regions of endogenous chromatin during integration. The LEDGF/p75 protein consists of 530 amino acids and contains a chromatin-binding N-terminal region that has a Pro–Trp–Trp–Pro (PWWP) motif, two copies of the AT-hook DNA binding motif and a nuclear localization signal (Figure 6.13). A highly conserved region of the C-terminus of LEDGF/p75 binds to IN and is termed the integrase-binding domain (IBD).[114–118] The importance of LEDGF/p75 in HIV-1 replication has been demonstrated by numerous groups and it is well documented that alteration of the cellular co-factor by mutagenesis, knockdown, RNA interference or alteration of the nuclear localization signal sequence has a deleterious effect upon viral replication.[119–122] Furthermore, LEDGF/p75 has been reported both to stimulate HIV-1 IN enzymatic activity (both strand transfer and 3′ processing) and to protect it from ubiquitin–proteasome degradation.[123,124]

In 2005, the first high-resolution crystal structure of the dimeric catalytic core domain (CCD) of HIV-1 IN complexed to the IBD of LEDGF/p75 was disclosed.[125] Of particular interest was a small binding pocket located at the CCD dimer interface where the IBD of LEDGF/p75 contacted two IN subunits (Figure 6.14). Although many of the key contact amino acid residues were validated by site-directed mutagenesis, additional interactions between the full-length proteins were more extensive than observed in the crystal structure.[120] A majority of these additional residues reside at the interface of the IN subunits and may suggest a potential role of LEDGF/p75 with IN multimerization.[126] Overall, these findings established the framework for designing small-molecule inhibitors of the interaction of LEDGF/p75 with HIV-1 integrase.

Debyser and co-workers utilized structure-based design to develop a series of inhibitors based on the aforementioned co-crystal structure of HIV-1 IN CCD with the IBD of LEDGF/p75.[127] Initially they performed a virtual screen

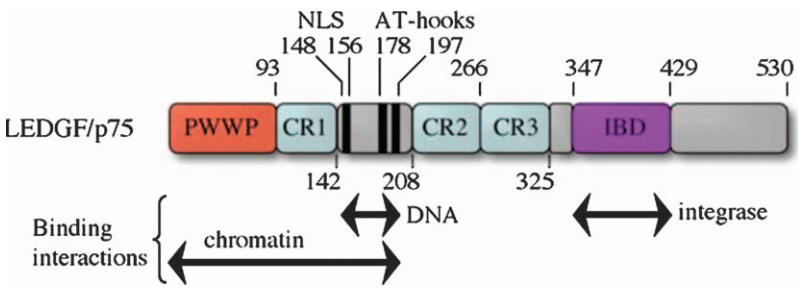

Figure 6.13 Domain organization of the LEDGF/p75 protein.
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