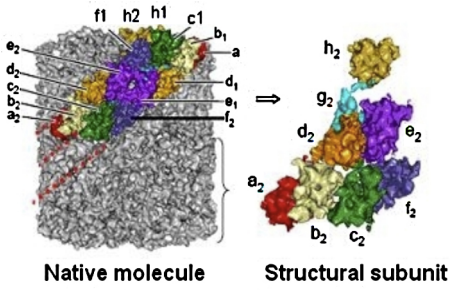
against the replication of influenza A virus is weaker. The antiviral activity seems to be due to the glycosylation of the structural subunits RvH1 and RvH2 and of the functional units as well, where the carbohydrate chains are exposed on the surface of the molecule and some of the moieties can bind to viral proteins. It is assumed that the complete molecules of the hemocyanins do not possess any antiviral activity because of the fact that in this case the carbohydrate chains are buried in between the whole molecule and therefore, are unable to interact with viral proteins. The antiviral activity is present only in the case when the carbohydrate chains are exposed externally.



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Novel Inhibitors of Nuclear Translocation of HIV-1 Integrase

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Infectious diseases, such as those caused by HIV remain highly significant health burdens world-wide, due to a lack of effective treatments and the ability of many viruses to develop resistance to anti-viral agents. During the infectious cycle, specific viral proteins, including those from cytoplasmically replicating viruses, enter the host cell nucleus in order to perform functions essential to the viral lifecycle. A particularly intriguing example is HIV-1 integrase (IN), which plays an essential role in infection in integrating the HIV genome into that of the infected host cell. Most IN-based anti-viral compounds target IN/DNA interaction, but since IN must first enter the nucleus before it can perform these critical functions, nuclear transport of IN is also an attractive target for therapeutic intervention. Here we describe a novel screening assay (Wagstaff et al., 2005, 2010) for identifying inhibitors of protein nuclear import, based on amplified luminescent proximity homogeneous assay (AlphaScreen) technology, which is high-throughput, efficient and cost-effective. We use the assay to screen for and identify specific inhibitors of the interaction between IN and its nuclear transport receptor Importin (IMP) α/β. Importantly, we demonstrate that one of the identified compounds, Mifepristone (Mif), is effective in preventing active nuclear transport of IN in transfected cells, and hence may represent a useful anti-HIV therapeutic. The screen also identified broader-spectrum inhibitors of IMPα/β such as Ivermectin (Ive), which will be useful tools for nuclear transport research in the future. That the activity of Mif and Ive can be validated in living/infected cells underpins the utility of this novel screening approach.

References

Wagstaff, K.M., et al., 2005. Anal. Biochem.
Wagstaff, K.M., et al., in press. J. Biomol. Screen.

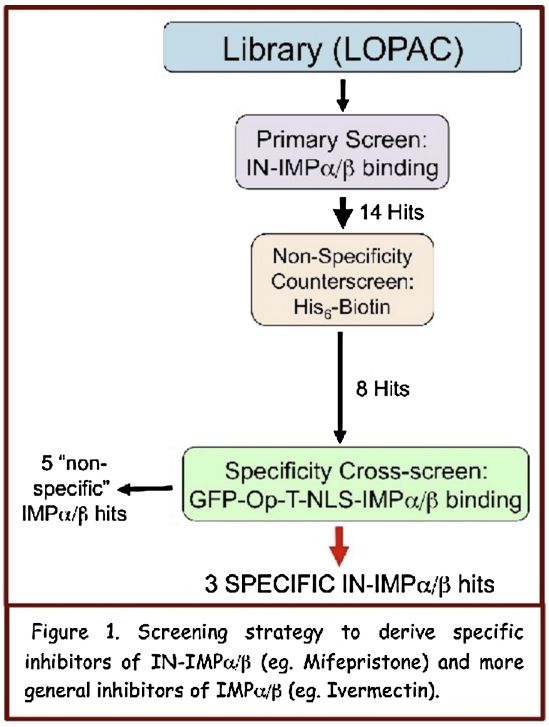

Figure 1. Screening strategy to derive specific inhibitors of IN-IMPα/β (eg. Mifepristone) and more general inhibitors of IMPα/β (eg. Ivermectin).

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Development of Antimicrobial Peptides as Topical Microbicides for the Prevention of HIV

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In the absence of an effective HIV vaccine, topical microbicides represent an important strategy for preventing the sexual transmission of HIV, the predominant mode of HIV transmission worldwide. Women now account for 46% of all adults living with HIV worldwide. The dynamics of the epidemic demand the development of safe, effective and acceptable female-controlled chemical and physical barrier methods, including topical microbicides, to reduce HIV transmission. An approved vaginal microbicide does not yet exist despite extensive development efforts. Although the field of microbicides had its first success with an approved NrTI (Tenofovir) and continuing development seems to focus heavily on other approved therapeutics (Dapivirine and Maraviroc), other strategies should continue to be explored. We have identified HIV-1 and HSV-2 inhibitory mammalian antimicrobial peptides (AMPs) through extensive evaluation of diverse peptides included in a unique AMP database developed at The University of Nebraska Medical Center. Several lead peptides from the database, as well as derivative peptides rationally engineered to enhance efficacy and reduce toxicity, have been identified with significant anti-HIV-1 and anti-HSV-2 inhibitory potential. These lead AMPs have been further evaluated in microbicide-specific mechanism and range of action evaluations, including virus transmission inhibition assays as well as activity in the presence of seminal and vaginal fluids. These data would suggest that the peptides act at an early stage of replication (inactivation, entry or RT) and against all virus subtypes. We believe that antimicrobial peptides have the potential to