

Novel HIV inhibitors developed against viral protein nuclear transport

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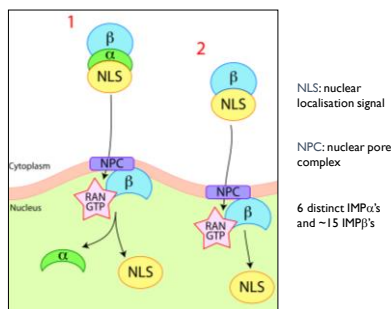
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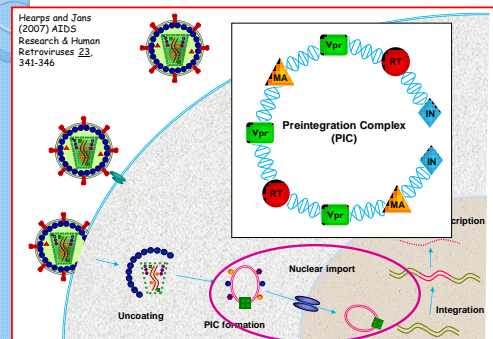
Nuclear Import Is an Anti-viral Target

- Viral disease is one of the greatest burdens of disease worldwide
- Lack of effective treatments:
 - Development of resistant strains
 - Cytotoxicity
 - Availability/High cost
- Urgent need for new therapeutics against novel targets
- Nuclear protein import is critical to infection by viruses including HIV, RSV, Dengue, Hendra, Rabies

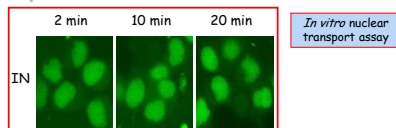
Nuclear Protein Import



HIV Lifecycle

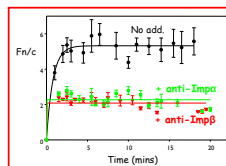


IN Nuclear Import is mediated by IMP α/β *in vitro*



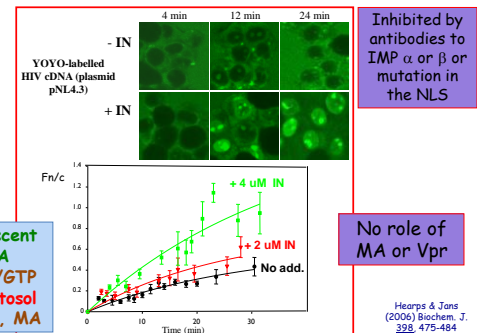
Fluorescent IN
+ ATP/GTP
+ cytosol
+/- Inhibitors
Antibodies

No effect of anti-IMP7, anti-IMP2 *etc.*

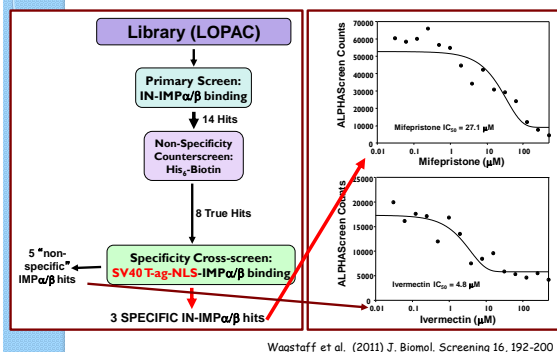


Hears and Jans (2006) Biochem. J. 398, 475-484

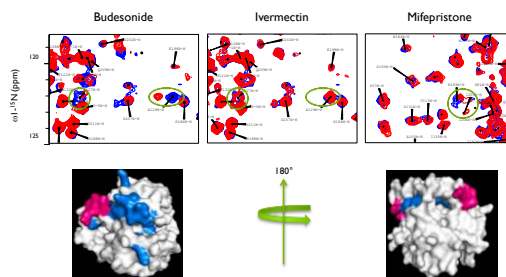
IN can facilitate nuclear uptake of HIV DNA



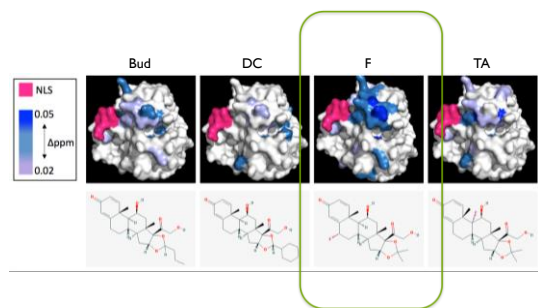
Screening for Nuclear Import Inhibitors



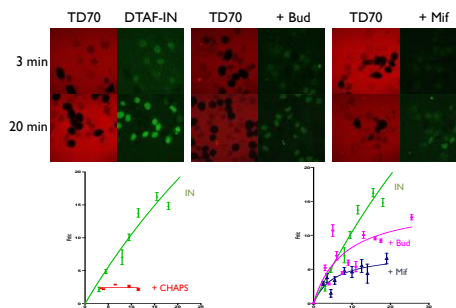
IN-specific inhibitors but not the general inhibitor Ivermectin bind to IN (NMR)



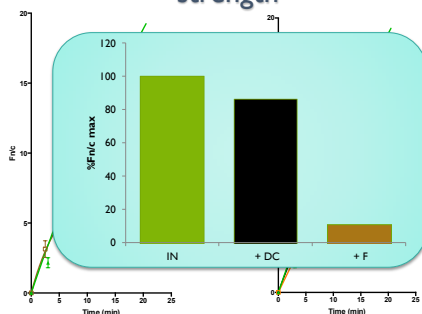
Inhibitor analogues bind to IN to varying extents



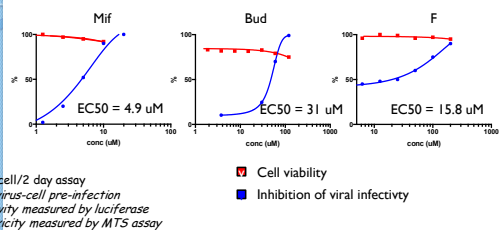
Nuclear transport inhibitors reduce IN nuclear accumulation



Compound analogues inhibit IN nuclear transport relative to IN binding strength



Inhibitors of IN Nuclear Import Reduce HIV Infection



Conclusions

1. Nuclear transport is a viable target for the development of anti-virals.
2. Structural studies demonstrate different binding sites and affinities for different compounds- clustered around the NLS
3. IN nuclear transport inhibitors represent a novel class of anti-HIV antivirals (potential for broad spectrum inhibition)



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