Reviewer’s report

Title: Novel therapeutic strategies targeting HIV integrase

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Reviewer: Peter Cherepanov

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“Novel therapeutic strategies targeting HIV integrase” by Quashie Sloan and Wainberg:

This is an excellent and timely review of the HIV IN inhibitor development. In particular, the clinical side (results of clinical trials, side effects and viral resistance) is covered extremely well. However, I feel that the structural aspect of the story may need a little bit more attention. The present version of the manuscript gives somewhat confusing and incomplete picture of the STI mode of action. For example, it is accepted in the field that the early co-crystal structure of 5CITEP (described on p3-4) with HIV IN catalytic core domain does not reflect how DKAs bind to the active site. On the other hand, the recent PFV structures, which explained how STIs actually work, are only mentioned in passing (p. 14) and appear to be mis-referenced. Just a few remarks on the subject would be sufficient to make the review more complete.

Specific comments

p.3: I am not sure if “phosphotransferase” is the right term. Like transposases, RNase H, etc., IN is a “nucleotidyltransferase”.

5CITEP structure may be right on how the compound bound to HIV-1 IN CCD in a crystal, but it certainly does not explain how STIs bind to and inhibit the functional IN-DNA complexes.

p10: “R148R” typo (twice on this page).

p12: dissociation time (t1/2) is a kinetic term, not equal to affinity (= an inverse of Kd). Use “tight binding”, “slow dissociation”, etc when referring to t1/2.

Even after re-reading “In this mode, an inverse relationship…” I am still not sure what it means. The sentence appears to suggest that in some cases slower dissociating compounds are less potent. Is that true?

In the third sentence of the second paragraph (“In these assays..”), it might help to indicate that the t1/2 values are given for the WT enzyme. Overall, this paragraph may need a little bit of work. I think the fact that there seems to be a correlation between slow off-rate from WT IN (i.e. tighter binding) and activity against RAL-resistant viruses (in particular N155H and Q148H/R) may deserve highlighting. Here, Merck’s data for MK2048 may also be cited (Grobler et al., 2009 - HIV integrase inhibitor dissociation rates correlate with efficacy in vitro. Antivir Ther 14(Suppl 1):A27). On the other hand, the fact that there is a
correlation between tighter binding and activity (on the same IN) is really a trivial point, which hardly needs a whole paragraph to elaborate.

P13: since the structure for GSK126744 cannot be shown in Fig.1, I would suggest removing the link to Fig. 1 here (last sentence on page 13).

P14: Please check references carefully. The structure of the intasome was in Hare et al., Nature 2010 (not ref 79); The STC/TCC structures in Maertens et al., Nature 2010. STI co-crystal structures were in Hare et al. PNAS 2010; Hare et al., Mol Pharmacol., 2011. There were several follow up papers, which included HIV models based on PFV structures. One of the important “modeling papers” was Krishnan et al., PNAS 2010 (+ few more important papers) – this paper is cited but in a wrong place. One recent work that feel deserves a special mention here is Johnson et al., 2011 (PubMed 22037850). In this work, authors were able to predict potency of STIs based on MD simulations of PFV-derived models...

P16: It has been shown that LEDGF is in fact NOT essential for HIV integration. See for instance Shun et al., 2007 (PubMed 17639082), which described and characterized HIV-1 integration in LEDGF-null cells. More recent data from Debyser’s lab with human LEDGF-null cells fully agree with this point (reported at meetings). Although it would be correct to say that LEDGF is a critical co-factor; that integration is greatly impaired in the absence, etc. etc.

BI are also LEDGF inhibitors. They do inhibit 3’-processing, but the mode of action is likely the same as of “LEDGINs”. (the binding site/mode is exactly the same). The antiviral activity of these molecules probably comes from both inhibiting interaction with LEDGF plus allosteric effects on the enzyme activity… It may be better to combine the 3'-processing and LEDGF inhibitors into one section (“Allosteric inhibitors”). The general definition of an allosteric inhibitor is “something that does not bind in the active site”. So even a clean LEDGF inhibitor is an allosteric inhibitor.

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests