Methods
In order to manipulate SAMDH1 levels using Vpx, different Vpx delivery systems were developed. These were virus-like particles (VLPs) packaged with different homologs of Vpx from SIV and HIV-2, and cell-penetrating peptides (CPPs) bound to either a 67 amino acid truncated SIVmac Vpx (67aaVpx) or to the WT full-length form. Two different CPPs were used in the synthesis: TAT and CPP44, the latter is based on a study by Kondo et al.3

Results
Upon treating different AML cell lines with the VLPs, we observed different SAMHD1-degradation capacities of the different Vpx homologs. Vpx from SIV isolated from macaques (mac239 and mac251) performed the best, compared to Vpx from other lineages. They also increased the ara-C sensitivity of THP-1 cells, which is an AML cell line with high SAMHD1 expression levels, up to 45-fold. Vpx from HIV-2 7312a only partially increased ara-C sensitivity, while HIV-2 Rod9 Vpx did not show any SAMHD1 degradation or improvement in ara-C sensitivity despite its high packaging efficiency in the VLPs.

As for the CPPs, CPP44 bound to 67aaVpx showed better uptake and SAMHD1 degradation compared to the TAT bound 67aaVpx in THP-1 cells. Upon co-treatment with ara-C, up to a 5-fold reduction in IC50 was observed when treated with CPP44-bound 67aaVpx. In an attempt to increase efficiency, full-length Vpx-bound CPPs will be prepared, and trials using these CPPs are currently underway.

Conclusion
We demonstrate that inducing SAMHD1 degradation by Vpx delivered via VLPs or CPPs efficiently improved ara-C sensitivity in AML cell lines. Since the VLPs presented a better efficiency compared to the CPPs, we are currently testing their efficiency in primary AML blasts, ex vivo. Ultimately, combining a Vpx delivery system with treatments containing ara-C could improve treatment outcomes in high-SAMHD1 expressing patients who fail to respond effectively to ara-C treatment.

REFERENCES

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