Ritonavir, nelfinavir, saquinavir and lopinavir induce proteotoxic stress in acute myeloid leukemia cells and sensitize them for proteasome inhibitor treatment at low micromolar drug concentrations

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BACKGROUND
Protein metabolism is an innovative potential therapeutic target for AML. Proteotoxic stress (PS) sensitizes malignant cells for proteasome inhibitor treatment. Some HIV protease inhibitors (HIV-PI) induce PS and may therefore be combined with proteasome inhibitors to achieve PS-targeted therapy of AML.

METHODS
We investigated the effects of all nine approved HIV-PI alone and in combination with proteasome inhibitors on AML cell lines and primary cells in vitro.

RESULTS
Ritonavir induced cytotoxicity and PS at clinically achievable concentrations, and induced synergistic PS-triggered apoptosis with bortezomib. Saquinavir, nelfinavir and lopinavir were likewise cytotoxic against primary AML cells, triggered PS-induced apoptosis, inhibited AKT-phosphorylation and showed synergistic cytotoxicity with bortezomib and carfilzomib at low micromolar concentrations. Exclusively nelfinavir inhibited intracellular proteasome activity, including the β2 proteasome activity that is not targeted by bortezomib/carfilzomib.

CONCLUSIONS
Of the nine currently approved HIV-PI, ritonavir, saquinavir, nelfinavir and lopinavir can sensitize AML primary cells for proteasome inhibitor treatment at low micromolar concentrations and may therefore be tested clinically toward a proteotoxic stress targeted therapy of AML.

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