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Screening of a library of newly synthesised purine analogues with focus on the treatment of acute myeloid leukaemia (AML)

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Purine analogues are already successfully installed in leukaemia, especially AML, treatment. Therefore, we used BrdU- and Resazurin-assays to survey the cytotoxic and cytostatic behaviour of our newly synthesised purine analogues in THP-1 cells. In this regard we found 4 interesting purine analogues, which also revealed structural connections between effective purine analogues. Three of these purines showed significant decreases in proliferation without any effect on the viability of THP-1 cells. Worth mentioning is IVA007, which besides a decline in proliferation also caused, even if not significant, cytotoxic effects. These results indicate that our selected purine analogues are mainly cytostatic compounds. Furthermore, purine analogues are in general OAT1 substrates and interactions were investigated performing transport survey with radio-labelled PAH. For this purpose, an OAT1 adenovirus was produced and transduced in HeLa and MDCKII cells. In this analysis several transport interactions of
our purines with OAT1 were discovered. On the one hand we surveyed IVA007 and IVA015, which inhibited the transport of PHA by OAT1 significantly and on the other hand we discovered purines without any influence on OAT1 transport, such as IVA060. Cell specific transport interactions were discovered with IVA056, which has influence on PAH transport in polarised (MDCKII) cells but not in nonpolarised (HeLa) cells. Moreover, we investigated the influence of OAT1 expression on the antiproliferating effect of our selected purine analogues. In doing so we detected one purine analogue, IVA007, whose cytostatic effect increased due to the presence of OAT1 in THP-1 cells. Therefore, the idea arise to apply purine analogues in combination with transporters, which would increase the cellular uptake of the drug and hence the specifity and effectiveness of chemotherapeutical agents.

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