Species Differences and Substrate Specificity of CYP3A Heteroactivation
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Purpose
Many reports have elucidated the heteroactivation of CYP3A substrate in in vitro study, while species differences and the substrate specificity of this heteroactivation remain unclear. The purpose of this study was to clarify the substrate specificity and the species differences of the heteroactivation, and evaluate the effect of heteroactivation on in vivo pharmacokinetics using animals.

Methods
The effects of activators including new chemical entities and commercial drugs on metabolism of CYP3A substrates, midazolam, testosterone and nifedipine were investigated using rat, monkey and human liver microsomes. Efavirenz that remarkably activated midazolam 1′-hydroxylation in in vitro study was used to evaluate the in vivo effect of heteroactivation on pharmacokinetics of midazolam.

Results
Although both midazolam and nifedipine oxidation were activated in human microsomes, there is a low correlation between the activation for the metabolism of midazolam and nifedipine. Meanwhile, 6β-hydroxylation of testosterone was not activated in human liver microsomes. Since efavirenz remarkably activated midazolam 1′-hydroxylation in human microsomes, the species differences of this heteroactivation were investigated. Efavirenz activated CYP3A-mediated midazolam 1′-hydroxylation in a concentration-dependent manner in the monkey and human liver microsomes, while efavirenz had no effect on midazolam 1′-hydroxylation in rat liver microsomes. In in vivo study using monkeys, the pretreatment with efavirenz caused 2-fold increase in the area under the curve (AUC) of 1′-hydroxymidazolam. However, the AUC change of midazolam by efavirenz was insignificant with only 20% decrease and therefore, the effect of heteroactivation observed in in vitro study on in vivo pharmacokinetics of midazolam is not completely clear.

Conclusion
Through this study, we elucidated species differences of heteroactivation by efavirenz. Although in vitro to in vivo extrapolation of heteroactivation remains uncertain in this study, heteroactivation exhibited high substrate specificity. This result suggested that the risk of drug-drug interactions through heteroactivation for whole CYP3A substrates might be limited compared to CYP3A induction.