Poster: Comparison of Metasite and StarDrop Prediction of CYP3A4, CYP2C9 and CYP2D6

Written by Young Shin
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Young Shin and his colleagues at Genentech presented this poster at the ISSX North American Regional meeting in Baltimore, MD in October 2009.

COMPARISON OF METASITE AND STARDROP PREDICTION OF CYP3A4, CYP2C9 AND CYP2D6 V. Sashi Gopaul, Young Shin, Hoa Le, Matthew Baumgardner, Cornelis Hop and Cyrus Khojasteh Drug Metabolism & Pharmacokinetics, Genentec, Inc, South San Francisco, CA, USA, 94080

Metabolite identification studies play an important role in determining the sites of metabolic liability of new chemical entities (NCEs) in drug discovery. However, generating these complex and detailed studies in a highthroughput environment is often a challenge. Therefore, the use of in silico tools that can predict the sites of metabolism of an NCE could enhance the drug design process. In this study we compare the utility of MetaSite and Stardrop, two predictive softwares available for this purpose...

MetaSite is a predictive software for the identification of regioselectivity of metabolism by major P450 isoforms. StarDrop is a data mining software that includes an in silico modeling feature to predict the regioselectivity and site of metabolism by CYP3A4, CYP2D6 and CYP2C9 only. Neither software can predict non-P450 catalyzed metabolism nor the rates of metabolism. Our objective was to evaluate the accuracy of MetaSite and StarDrop to predict the site of oxidation by CYP3A4, CYP2D6 and CYP2C9. Altogether, 12 substrates of CYP3A4, 9 substrates of CYP2C9 and CYP2D6 were each analyzed by each software and the results were compared[1]. To measure the degree of prediction by each software, we assigned 3 points if the first major metabolite reported is predicted correctly, 2 points for the second choice and one point for the 3rd choice. No points were given for the 4th choice and beyond. The total points assigned for each enzyme experimentally were compared as a percentage of the total points assigned theoretically for a first choice prediction for all substrates for each enzyme. Our results show that MetaSite and StarDrop are similar in predicting the correct site of metabolism for CYP3A4 (86% vs 83%). StarDrop appears to do better in predicting the correct site of metabolism by CYP2C9 and CYP2D6 metabolism (89% and 93%, respectively) compared to MetaSite (59% and 70%, respectively). We are currently assessing the accuracy of MetaSite and StarDrop predictions of NCEs with in-house experimental observations.

[1] David F.V. Lewis* (2003) Current Medicinal Chemistry, 2003, 10, 1955-1972

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A copy of their poster as available as a [PDF](#) .