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High-throughput metabolic stability assays using rapid fire and accurate-mass spectrometry

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Metabolic stabilities of small molecules, in the presence of liver microsomes and/or hepatocytes, have been frequently assessed during lead optimization in the early drug discovery process. The resultant ranking is a key selection criterion for compound advancement into *in vivo* studies because a more metabolically stable compound will likely give rise to a longer half-life in animal studies. *In vitro* metabolic stability studies have been routinely performed using pooled liver microsomes from various species (human, monkey, dog, rat and mouse). The key detection technology of this assay is by monitoring the turnover of the compound in the presence of liver microsomes using liquid chromatography-tandem mass spectrometry (LC-MS). However, the bottleneck of the assay falls on the long separation time in LC. The use of RapidFire, a system consisting of a solid-phase extraction column, automated plate handler, sample injector, and software interface with MS, has significantly improved the throughput. In addition, the use of an Accurate-Mass Quadrupole Time-of-Flight (QTOF) MS system with RapidFire eliminates the need of tuning prior to sample analysis and further streamlines the MS analysis process. In this report, we describe the implement of RapidFire-QTOF system in human and rat metabolic stability assays, resulting in a throughput ten times higher than the traditional LC-MS method without compromising data quality.

Biography

Paul Lee joined Amgen Inc. in 2004. He currently leads a group of scientists and is responsible for developing biochemical and cellular assays, implement high-throughput screens and lead discovery in the early drug discovery process. Prior to joining Amgen, he held various positions at Pfizer, Pharmacia, and Glaxo-Wellcome for over 12 years. He received his PhD in Pharmacology from University of Hong Kong and completed his Postdoctoral training at NIH.

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