Society of Toxicology 52nd Annual Meeting & Toxexpo 2013
March 10-14, 2013, at the Henry Gonzalez Convention Center,
San Antonio, TX, USA

1819 Effects of Tyrosine Kinase 2 Inhibitors on Megakaryocyte Development.

H. Uppal1, D. Danilenko1, E. Harstad1, J. Tarrant1, E. Clarke2, P. Dhawan1, A. Kauss1, B. McCray1, D. Misner1 and J. Singh1. *1Safety Assessment, Genentech Inc., San Ramon, CA; 2ReachBio LLC, Seattle, WA.*

Background: Tyrosine Kinase 2 (Tyk 2) is a member of the Janus Activated Kinase (Jak) family. Tyk 2 is associated with signaling of pro-inflammatory cytokines, IL-12 and IL-23. Therefore, inhibition of Tyk 2 may potentially treat inflammatory diseases such as inflammatory bowel disease (IBD), rheumatoid arthritis, and psoriasis. Tyk 2 is also activated during thrombopoietin signal transduction, a pathway necessary for megakaryocyte development and platelet production. Studies were conducted in vitro and in vivo with potent Tyk 2 inhibitors with varying levels of JAK-family and general kinase selectivity to understand potential effects of these Tyk 2 inhibitors on platelet development.

Methods: Tyk 2 inhibitors were evaluated in vitro in human, mouse and cynomolgus monkey megakaryocyte colony forming cell assays. General cytotoxicity was evaluated by measuring cellular ATP levels. Direct effects of Tyk 2 inhibitors on platelet function (aggregation), energetics (oxygen consumption), and viability (ATP levels) were also evaluated in vitro. The effect of Tyk 2 inhibitors on platelet number was evaluated in short term (5-10 day) mouse studies. Tyk 2 and Jak mRNA expression was evaluated in human megakaryocytes by quantitative PCR to understand target expression.

Results: Tyk 2 inhibitors caused a comparable reduction in the number of colony forming cells and the viability of megakaryocytes from human, mouse and nonhuman primates. There were no direct effects of Tyk 2 inhibitors on the aggregation capacity, oxygen consumption, or ATP levels of human platelets in plasma. Tyk 2 inhibitors caused platelet reduction in mice. Tyk2 and Jak 1, 2, and 3 were comparably expressed in human megakaryocytes.

Summary: The in vitro and in vivo findings demonstrate that platelet reductions caused by multiple Tyk 2 inhibitors (with varying selectivity against other Jak family kinases) are likely due to effects on megakaryocyte development.