2008 Spring Dinner Meeting Review

by Greg Brorby

The GETA Spring dinner meeting was held at the Terrace Café in Millbrae on April 3, 2008. The featured speaker was Dr. Dinah Misner of Roche Palo Alto, LLC. The topic was "Strategies to Predict QT Prolongation and Arrhythmias: Assessing hERG and Other Cardiac Ion Channels Early in Drug Development."

Dr. Misner presented preclinical strategies to assess new chemical entities (NCEs) for cardiovascular liabilities early in the development process, with an emphasis on detection of QT prolongation and arrhythmias. Specifically, although drug-induced prolongation of the QT interval is common, in rare cases, it may lead to a form of ventricular tachyarrhythmia known as torsades de points (TdP). Several drugs have been withdrawn for TdP, and numerous others have been denied approval, discontinued for development, or labeled for their TdP propensity. Since 2005, FDA has specifically required preclinical assessment of QT prolongation, including an *in vitro* I_{Kr} (hERG) assay, which determines the ability of a chemical to block the function of the hERG channel, and *in vivo* QT assay. Dr. Misner discussed recent advances in the hERG assay, which significantly increases the throughput compared to conventional methods, thereby allowing testing of more compounds earlier in development. She also discussed several factors that need to be taken into account when interpreting hERG data (e.g., solubility, protein binding) and truths and misconceptions regarding assay results (e.g., hERG block does not necessarily lead to QT prolongation, QT prolongation does not necessarily lead to TdP) because the majority of compounds are positive in this assay. Dr. Misner also discussed several options to assess potential QT effects, including isolated heart assays, anesthetized guinea pig model, and conscious dog telemetry, each of which has advantages and disadvantages. In conclusion, Dr. Misner recommended placing a high priority on *in vitro/in vivo* safety pharmacology early in drug development, individualizing the "risk assessment" for each project and compound, and continuing research and/or refining predictive tools for cardiovascular risk.