Recent Progress from WP4

Work package 4 (WP4), the group responsible for biomarkers of drug-induced vascular injury (DIVI), is one of the three organ-based WPs that are part of the SAFE-T consortium. WP4 has to overcome an important hurdle as it develops its strategy for the qualification of DIVI biomarkers: DIVI in preclinical animal models is a toxicity that does not appear to have a corresponding finding in humans. In fact, the few drugs with preclinical DIVI that have advanced into clinical development have not been linked to similar findings in humans, and several drugs that produced DIVI in animal toxicity testing (*e.g.,* theophylline and minoxidil) have long-established clinical safety records. This lack of a direct clinical correlate poses several unique challenges for qualifying biomarkers of preclinical DIVI:

1. How should surrogate patient populations with vascular injury be identified?
2. What "gold standard" should be used for determining biomarker performance?
3. Should candidate biomarkers be selected based on known association with preclinical DIVI or can biomarkers of vascular injury in humans be used to guide biomarker selection?

To address the first question, the team proposes to use surrogate populations of patients suffering from diseases in which histopathologic findings are similar to the ones observed in preclinical DIVI. Those populations include patients with various vasculitides (*e.g.,* Takayasu disease, Behçet's disease, hypersensitivity vasculitis, etc.) and other vascular disorders (e.g. diabetes, coronary artery disease, etc.). Regarding the second question, when determining the performance of a novel biomarker, a comparison is typically made to the conventional gold standard for the disease or toxicity being investigated. For example, novel biomarkers for drug-induced liver injury might be compared to ALT, whereas drug-induced kidney injury biomarkers would be compared to BUN and/or creatinine. However, the lack of a current/gold standard for the assessment of preclinical DIVI in humans requires a different approach to studies for characterization of biomarker candidates and for the qualification of vascular biomarkers. We propose using the current diagnostic criteria for our surrogate populations with human vascular injuries as the basis for determining biomarker performance. Finally, candidate biomarkers have been selected on the basis of both preclinical and clinical data, which will require both a "forward and reverse" translation approach. The forward translation process will qualify the selected preclinical candidate DIVI biomarkers in patients with selected vascular pathologies, whereas for reverse translation the WP4 team has selected biomarker candidates of human idiopathic vasculitides and will test them in preclinical models of DIVI.

A detailed description of WP4's strategy for qualifying biomarkers of DIVI was submitted to the IMI-JU in June, 2010. The 44-page document was reviewed by two independent consultants and their constructive comments were shared with the WP4 team in January, 2011. As a result of the review process the DIVI strategy was formally endorsed by the IMI in June. This approval marks a significant milestone for WP4 since the original endorsement of the SAFE-T consortium in 2009 included a provision that WP4 must submit a strategy plan at Month 12 in order to receive continued funding. We congratulate WP4 on this accomplishment!

To further explain and promote our translational strategy, Silvia Guionaud of Pfizer presented a poster titled "Histological Comparisons of Clinical and Non-clinical of Drug-induced Vascular

Injury to Support Qualification of Translational Biomarkers" at the 30th annual meeting of the Society of Toxicologic Pathology in Denver, Colorado (June 19 to 23). The poster provided an overview of the WP4 strategy, supported by a tabulated overview of morphologic changes associated with human vasculitides compared to preclinical DIVI, as well as numerous corresponding histologic images with descriptions. Preliminary biomarker results from reverse translational studies in Pfizer Sandwich were also included. There was lively interest in the poster, and numerous electronic copies were sent out to interested conference attendants. A poster that more broadly described the SAFE-T consortium and the WP4 strategy was also presented at the 50th annual Society of Toxicology meeting on Washington DC in March, 2011.

If this project is successful, and qualified safety biomarkers for decision making in translational and clinical contexts are accepted by regulatory heath authorities, the result could be the faster approval of safer and novel drugs. This is particularly important for drugs that cause preclinical DIVI, a toxicity that can lead to the early termination of drug development because of the lack of clinically relevant biomarkers.