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PROJECT PROPOSAL

Topic: Genomic Analysis of Cancer SignalingP (Hedgehog, Notch, Wnt) Important in Stem Cell Maintenance and Renewal as a Predictor of Cancer Risk Following Subchronic Exposure to Environmental Carcinogens

Submitted by: Dr. Don Delker and Dr. William Ward, U.S. Environmental Protection Agency, Durham, NC

The identification of common key events in the development of cancer following environmental chemical exposure is of utmost importance to the regulatory community. Use of common key events in the risk assessment process provides a stronger framework for making accurate comparisons among chemical classes as well as facilitates the estimation of cumulative risk. Measurement of permanent alterations to cellular DNA have for many years been the standard for estimating cancer risk to environmental chemicals. However, not all chemical carcinogens damage DNA and the prediction of carcinogenicity of non-genotoxic chemicals has been problematic. Because cancer is considered a disease of clonally expanded de-differentiated cells with stem cell like properties, the genomic analysis of signaling pathways involved in stem cell maintenance and renewal *in vivo* might provide a useful alternative for estimating cancer risk following short term environmental chemical exposure. Several well studied signaling pathways important in stem cell maintenance and renewal are commonly deregulated during carcinogenesis including Hedgehog, Notch, and Wnt pathways. These pathways are transiently activated to promote stem cell self-renewal in normal tissues whereas continuous activation is associated with the development of many types of human cancer. Therefore, the genomic characterization of alterations in these pathways in response to environmental chemicals could provide a means for which researchers might predict the potential carcinogenicity of chemical agents after short term *in vivo* exposures (<30 days). Previous work from our laboratory and others have identified alterations in the Wnt signaling pathway in target tissues as early as two weeks following chemical carcinogen exposure while little or no change was observed in this pathway following non-carcinogen exposure (Glatt et al. 2005 and Ward et al. 2006). The observed alterations in Wnt signaling gene transcripts were also dose-dependent and correlated well with the relative potency of the chemical carcinogen. In this proposal we describe research objectives that will facilitate the genomic characterization of alterations in these signaling pathways as predictors of the carcinogenic potential of environmental chemicals.

We propose research initiatives in three main areas:

1. Mine existing databases of gene expression profiles generated *in vivo* by known chemical carcinogens or non-carcinogens for evaluation of Hedgehog, Notch, and Wnt pathway activation.
2. Categorize genes acting in concert in each signaling pathway with respect to concurrent up-regulation or down-regulation for estimation of gene clusters that might be useful in risk assessment.
3. Evaluate the impact of uncharacterized gene transcripts on Hedgehog, Notch, and Wnt pathway activation *in vitro* using stably transfected cell lines.

Potential Impacts of This Project are as follows:

1. Provide an alternative means whereby environmental chemicals might be classified as carcinogenic or non-carcinogenic based on their sustained activation of Hedgehog, Notch, and/or Wnt pathway activation critical to the expansion of deregulated stem cells.
2. Provide important information regarding gene clusters that are transcriptionally co-regulated by carcinogen exposure that can be used as weight of evidence in the cancer risk assessment process.

To our knowledge, this issue is not being addressed by any other organization or forum.

References:

1. WO Ward, DA Delker, JW Allen, DC Wolf, S Hester, S-F Thai, and S Nesnow (2006) Toxicol Pathol, 34:863-878.
2. CM Glatt, M Ouyang, W Welsh, JW Green, J O'Connor, SR Frame, NE Everds, and DA Delker (2005) Environ Health Perspect, 113:1354-1361.