



NIEHS Conference Report

Epigenetic Actions of Environmental Arsenicals

September 20-22, 2012 / Tucson, Arizona

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Rationale and relevance to SRP: Arsenical exposure is an American as well as global health concern. Arsenic is one of the most widespread environmental toxicants to which humans are exposed - primarily through drinking water and food, with other routes of exposure such as from air, soil, and medications playing a smaller role. The routes of exposure are decidedly dependent upon local conditions. Over the past 50 years, epidemiological studies have convincingly linked the level of arsenic exposure to human cancers of the lung, urinary-tract, and skin. Prostate, kidney, and liver cancers have also been associated with arsenic, but the supporting data is more limited. Based on the epidemiological data, the International Agency for Research on Cancer (IARC) has classified arsenic and arsenic compounds as group 1 human carcinogens, and the World Health Organization has set a guideline advising that arsenic concentrations in drinking water should not exceed 10 ppb or 10 µg/l. Arsenicals may have multiple mechanisms of carcinogenic action; however, epigenetic remodeling represents an emergent mechanism by which arsenicals may act. Of course, the epigenetic changes are complex and the mechanisms that control these aberrant changes remain enigmatic. A major goal of this workshop was to integrate distinct scientific perspectives into a cohesive transdisciplinary understanding of the epigenetic consequences of environmental arsenic exposure.

Optimizing interactions: The workshop participants were selected to ensure a significant breadth of scientific expertise that stretched from population biology to in vitro model systems to high throughput epigenetic technologies – essentially from molecules to humans. The participants represented the full range of the scientific career arc, from graduate students embarking on specific research projects to senior principal investigators who created broad new areas of biological inquiry. The meeting itself was structured to maximize the amount of interaction between the scientists assembled, with presentations and discussions from all participants. The workshop agenda was composed primarily of thematic scientific sessions, with three to five speakers per session. Each speaker was encouraged to share

unpublished data and ideas – to be bold and speculative, which a significant majority of presenters succeeded in. Ample time was provided for question and discussion periods after each presentation. Breakfast, lunch, and dinner were provided group style, and arranged in ways to stimulate one-on-one and small group discussions.

What we learned: Overall, a number of features of arsenical biology were reaffirmed and new directions towards a better understanding of the role of epigenetic mechanisms in arsenical carcinogenesis were discussed throughout the meeting. Cell biologists with signaling expertise provided insights on the systems that may impinge upon epigenetic control mechanisms, including redox regulation and EGFR. Multiple *in vitro* models of arsenical-mediated malignant transformation supported clear links towards a mechanistic role of epigenetic dysfunction, although legitimate concerns were raised regarding the temporal nature of arsenical exposure in these models. Presentations on new next-gen DNA sequencing technologies and its associated informatics provided exciting new approaches and directions for whole epigenome analysis in arsenical toxicology. These new technologies may prove valuable in overcoming the challenges in epigenetic biomarker development, presented in a number of presentations that involved “real world” human populations.

Outcomes: Selected participants of the workshop will author a paper describing the outcomes of the workshop discussions. This work will be prepared for publication in a formal setting, probably by first asking Environmental Health Perspectives (EHP) for a preliminary review as to appropriateness for publication, or alternatively through a rapid dissemination as a white paper on the University of Arizona SRP website.

