Human stem cell-based mutagenesis assay for accurate genotoxicity and MoA evaluation

The GenomeTox method for in vitro genotoxicity testing enables genome-wide genotoxic and mechanistic evaluation of virtually any mutational readout using a single assay, to support early de-risking and mechanistic elucidation of toxicity of new compounds and chemicals (Fig. 1). It uses human hematopoietic stem and progenitor cells (HSPCs) derived from umbilical cord blood (CB). These cells have extremely low levels of mutation load, providing a highly sensitive system in human setting. Employing whole genome sequencing with proprietary in-house developed analysis pipelines it surveys the entire genome, including mitochondrial DNA and telomeres, and as such enables truly comprehensive genotoxicity assessment, in contrast to currently available methods. The assay has been validated on a compendium of antiviral compounds, chemotherapeutics and ionizing radiation (Fig.2).

Key advantages

This novel genotoxicity assay provides several key advantages as it is:

• versatile: employing WGS it enables assessment of virtually any mutational readout including prediction of carcinogenicity potential, using a single assay,
• sensitive: using human cord blood-derived cells with negligible background mutation burden;
• relevant: based on the use of accessible primary human cells, supporting reliable translation to human subjects;
• accurate: the cells are obtained directly from tissue of origin and not immortalized, thus all relevant molecular pathways are completely intact.

Potential impact

GenomeTox assay to drive improved drug development

Attrition due to safety issues in preclinical and clinical drug development continues to represent a major cause of overall loss of projects relatively late into the development process. Although a battery of established assays is currently available, these often generate inconsistent results with much inter-assay variability, and demonstrate poor prediction of in vivo genotoxicity and carcinogenicity. The novel GenomeTox assay provides a solution for robust genotoxicity testing as well as prediction of carcinogenicity potential, to enable efficient early de-risking. As such it has vast potential to enable significant savings of resources of compounds that would otherwise fail much later in development, as well as successful development of compounds that might have been unnecessarily discontinued due to unclear or misinformed genotoxic potential.
A novel assay using primary human cord blood-derived HSPC for robust and genome-wide genotoxicity testing

**Image 1:** Schematic representation pipeline and key outcomes of the GenomeTox method for in vitro genotoxicity testing, employing primary human cord-blood-derived HSPC

**Image 2:** Comparison of GenomeTox analysis of a panel of antiviral drugs to current in vitro genotoxicity assays as well as in vivo carcinogenicity studies (golden standard). Red indicates the assay is positive for genotoxicity, i.e. the compound is identified as unsafe. Green indicates the assay is negative for genotoxicity, i.e. the compound is identified as safe. White indicates the compound is not tested using the indicated method. MLA: mouse lymphoma assay; HPRT: HPRT gene mutation assay; Micronuc test: micro-nucleus test; Chromos aberration: chromosomal aberration assay. Figure represents GenomeTox-generated data combined with data from Waters et al., (2022) Environmental and Molecular Mutagenesis 63:37-63.

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**Data**

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