

The National Toxicology Program (NTP) High Throughput Screening (HTS)
Initiative: Current Status and Future Directions

R. R. Tice¹; J. Fostel²; C. S. Smith¹; K. Witt¹; J. H. Freedman¹; C. J. Portier¹; A.
D. Dearry¹; J. R. Bucher¹

¹ NTP/NIEHS/NIH/DHHS, Research Triangle Park, NC, USA.

² Alpha-Gamma Tech., Raleigh, NC, USA.

Since mid-2005, the NTP has participated in the NIH Molecular Libraries Initiative (MLI) by collaborating directly with the NIH Chemical Genomics Center (NCGC) to use quantitative HTS (qHTS) assays to test compounds for activity against defined targets. This collaboration benefits to both programs by adding toxicity testing capabilities to the MLI, and by allowing rapid implementation of NTP's HTS program designed to screen large numbers of compounds for activity against targets and pathways believed to have toxicological relevance (e.g., oxidative stress, inflammation, apoptosis). The NTP plans to link HTS-produced toxicity data to data from standard in vivo toxicological assays, with the goal of identifying mechanisms of action requiring additional investigation, developing predictive models for biological response, and prioritizing substances for further evaluation. In addition to the collaboration with NCGC, a medium throughput screen using *Caenorhabditis elegans* has been established to provide in vivo data on the same chemicals screened at the NCGC. Another aspect to this collaborative effort is a joint NTP/EPA faculty that shares ideas and strategies and provides a broader venue for scientific debate on HTS. The NTP had provided 1353 unique compounds (55 in duplicate to assess assay reproducibility) with known toxicological effects to the NCGC (see C. Smith et al. poster). The NTP has also provided six cell-based HTS assays to the NCGC; these assays evaluate cytotoxicity (2), caspase activation (3), and a cell membrane efflux pump (1). The first set of NTP compounds has been tested in several of

these assays in up to 7 human and 6 rodent cell types (see M. Xia et al. Poster). The resulting data are posted on PubChem and are being evaluated internally by the NTP for patterns of response potentially indicative of toxicological effects. Efforts are underway to identify other potentially useful assays and the second set of ~1408 compounds.