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In the development of new medicines, toxicity is a major cause of early clinical failures. Although many in vitro cell-based assays have been developed for predicting in vivo toxicity, high throughput in vitro cell-based assays that are predictive of in vivo toxicity have not been widely applied in large-scale chemical libraries. This proposal describes a high-throughput cell-based assay using luminescent yeast (yVC) to predict the toxicity of 1,000 drug candidates. YVC is a suspension-grown microorganism that contains the luciferase reporter gene under control of the galactose inducible promoter. We have validated yVC as an effective high-throughput system for identifying drug-specific induction of the luciferase reporter gene after treatment with a diverse panel of chemical compounds. Using yVC, we have established profiles of toxicity for five common chemicals and have predicted toxicity for an additional 500 chemicals. Using these data, we anticipate being able to predict toxicity for almost 1,000 compounds by developing a corresponding profile for each drug. We intend to make the yVC toxicity profiles available to the scientific community and will derive novel hypotheses for in vitro activities for 1,000 compounds that could contribute to their toxicity. In addition, we anticipate that yVC will have broad utility in a variety of systems, including toxicity assessment of bacterial populations, new in vitro drug discovery platforms, and for the discovery of metabolic inhibitors.

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