devTOX™ Assay FAQs

Stemina BIOMARKER DISCOVERY

What is devTOX?

The **dev**TOX suite of *in vitro* assays use either human embryonic stem (hES) cells or induced pluripotent stem (iPS) cells to provide a signal of a test article's potential to disrupt human development.

How should the assays be used?

devTOX^{qP} can be used to screen and prioritize a series of compounds to determine which compound has the lowest developmental toxicity potential. Due to its high concordance with required animal models, **dev**TOX^{qP} can be used as part of the workflow to reduce animal testing.

devTOX DISCOVERY should be used when information about potential mechanisms of toxicity or disrupted pathways by the tested compound is desired.

During which stage of a compound's development should the assays be used?

Most often, the **dev**TOX assays are used early in the discovery phase for a series of molecules after they have been deemed active. The **dev**TOX^{qP} assay can be used to provide information regarding the concentration at which the test compound has the potential to elicit developmental toxicity. **dev**TOX^{qP} and **dev**TOX DISCOVERY aid in decision-making prior to much more costly and time-intensive preclinical *in vivo* studies.

Why do you offer both hES and iPS cell types?

Stemina offers two cell types to provide flexibility in choosing the cell type that best serves the scientific or regulatory/policy requirements of our clients.

Which is more effective: hES or iPS cell types?

Experiments comparing the compound predictions from the **dev**TOX^{qP} model have shown that both iPS and hES cells predict potential developmental toxicants with ≈85% accuracy. While slight differences have been identified between these two cell types, the scientific literature and our own internal studies have shown that these differences are minor. Studies performed at Stemina have shown a 97% concordance between the cell types.

Why use hES cells?

The assay was originally developed and optimized using WA09 hES cells. Of the available hES cell lines, this line is best characterized and used most often by researchers.

Why use iPS cells?

Some sponsors prefer iPS cells due to corporate policies or governmental regulations that preclude the use of hES cells.

How do I interpret the results across the eight exposure levels provided by the devTOX^{qP} assay if I don't know the likely therapeutic range early in the discovery phase of development?

The results should be considered in the context of the total information generated as compounds are advanced through testing, just as would be done with any discovery phase *in vitro* assay. If the tested compound shows no potential to act as a developmental toxicant, or indications of developmental toxicity are seen only at the highest exposure levels, this is important information as the likely therapeutic range or dose is established.

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devTOX^{qP}™ *quick*PREDICT

devTOX™ DISCOVERY

What are the benefits of using the devTOX suite of assays?

- Early identification and elimination of potential developmental toxicants may help to reduce time and cost of subsequent testing and aid in prioritizing a series of molecules for further development.
- The first and only human cell-based system available for developmental toxicity testing.
- Better predictivity than other *in vitro* and *in vivo* assays.
- Low cost.
- Small amount of test compound required.
- Quick turnaround time.

Who should be using devTOX^{qP}?

Any company that is developing new compounds for use in pharmaceutical, agricultural, industrial, tobacco, cosmetic, or consumer products that will have potential for human exposure.

How predictive are the devTOX assays for signaling the potential for developmental toxicity?

The assays are ≈85% predictive of developmental toxicant across a wide range of more than 100 chemicals. Accuracy may be higher or lower in certain categories of compounds.

Can the devTOX assays replace other developmental toxicity assays?

Yes. Based on the above benefits, **dev**TOX^{qP} has proven to be more predictive and less subjective than the zebrafish, whole embryo culture, and mEST assays. The data generated with the **dev**TOX assays presents an excellent opportunity to include an *in vitro* human endpoint in read-across or weight-of-evidence approaches.

Note: Under the current regulatory requirements, **dev**TOX *cannot* replace required standard *in vivo* mammalian studies, but can reduce the number of animals used by eliminating compounds from further testing.

The assays are unique in their ability to distinguish between cytotoxicity and potential for developmental toxicity. How do they stack up?

The **dev**TOX assays are based on very sensitive measurements of metabolic perturbation that can be observed at much lower exposure levels than general cytotoxicity. Each assay's ability to separate the two endpoints provides more information about the potential for human developmental disruption than cytotoxicity alone.

What if a compound elicits a metabolic response at the same concentration where cytotoxicity is observed?

This type of response can be more difficult to interpret and additional data can help put the results into context. In the absence of an additional data, this result can be interpreted as a positive response. If a compound is cytotoxic to hES or iPS cells, it would likely kill the cells in the developing embryo, which could lead to embryo lethality or malformations.

How predictive is the devTOX^{qP} assay of the outcome in required *in vivo* tests?

The **dev**TOX^{qP} assay is ≥ 80% concordant with the rodent and rabbit Segment II models for a set of compounds with a broad range of chemotypes.

How does devTOX^{qP} differ from devTOX DISCOVERY?

devTOX^{qP} is a tool that is best used for quick answers at low cost, using small amounts of compound. The assay can help make early decisions about potential developmental toxicity issues.

If a potential developmental toxicant is identified with **dev**TOX^{qP} or if there is interest in understanding mechanisms of toxicity or biological pathway information, **dev**TOX DISCOVERY can be used to help identify potential pathways and mechanisms responsible for the developmental toxicity.

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