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Predicting Skin Sensitization Using 21st Century Toxicology

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Abstract

Allergic contact dermatitis (ACD) is an adverse health effect from repeated exposure to skin-sensitizing chemicals. Regulatory authorities require tests, like the murine local lymph node assay (LLNA), to identify potential skin sensitizers. The Organisation for Economic Co-operation and Development (OECD) established an Adverse Outcome Pathway (AOP) for skin sensitization (1). To reduce or replace animal use, OECD is using the AOP as a framework for developing integrated testing strategies with novel *in vitro* and *in silico* approaches. The Tox21 and ToxCast projects include high-throughput screening (HTS) assays that map to key events in the AOP (e.g., oxidative stress, cytokines) (2, 3). We built a cross-validated random forest model using ToxCast Phase II data and a balanced training set of 60 chemicals with LLNA data. The model predicted LLNA results with 80% accuracy. The assays with highest variable importance included known AOP targets (e.g., Nrf2, T-cell proliferation) and targets outside the current AOP (e.g., Coll III, PPAR, PXR, ER). Well-characterized AOPs like skin sensitization provide opportunities to use HTS data to develop efficient testing strategies that minimize animal use in regulatory testing. This project was funded in whole or in part with Federal funds from NIEHS, NIH under Contract No.HHSN27320140003C.

References

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