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E-Morph Assay – an innovative image-based phenotypic screening assay for estrogenic and anti-estrogenic activity

Phenotypic screening assay, endocrine disruptors, estrogenic activity, environmental estrogens, environmental chemicals, HTS

INVENTION NOVELTY

Exposure to environmental chemicals, especially those that interfere with normal estrogen functions, can lead to adverse health effects including cancer or perturbed growth and reproduction. Consequently, adverse health effects that are caused by such endocrine disrupting chemicals (EDC) in the environment, food or consumer products are of high public concern. The identification and characterization of EDCs including substances with estrogenic activity still requires complex animal testing. The currently approved *in vitro* test systems each only address single mechanistic events of estrogen activity. Human-relevant functional assays that provide a more complete picture of the various mechanistic events were missing so far. The innovative high-throughput screening- (HTS) compatible and image-based phenotypic E-Morph Assay fills this gap. It facilitates robust measurements of the estrogenic and anti-estrogenic potential of environmental chemicals using quantitative changes in the cell-cell contact morphology of human breast cancer cells as a novel functional endpoint with clinical relevance.

VALUE PROPOSITION

Estrogen-dependent changes in the cell-cell contact morphology of adherens junctions influence cancer-related parameters such as cell adhesion, cell stiffness and cell motility. The E-Morph Assay provides a reliable and robust human-relevant phenotypic readout to determine estrogen signaling activity. It is established and optimized for automated HTS using local changes in the signal intensity of the cell adhesion protein E-Cadherin (E-Cad/GFP reporter) as a novel and efficient readout for estrogenic activity.

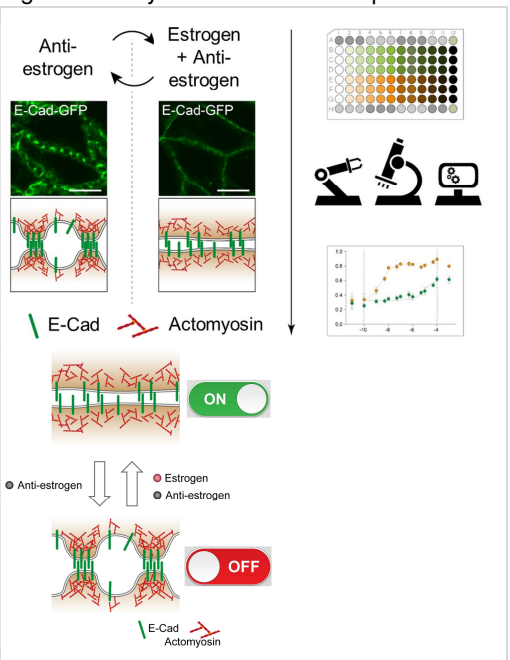

***Fig. 1**:Graphical representation of the phenotypic readout and screening workflow*

TECHNOLOGY DESCRIPTION

The conceptual design of the E-Morph Assay (see Fig. 1) is based on the competitive co-treatment of individual test substances with the anti-estrogen Fulvestrant. Treatment of MCF-7 breast cancer cells with Fulvestrant alone leads to a reorganization of adherens junctions and an increased, bubble wrap-like spacing between adjacent cells, along with an increase of cell stiffness and cell-cell adhesion, but a decrease in cell motility. These reorganization processes are attributed to a change in E-Cad distribution and signal intensity at adherens junctions. This phenotype can be prevented by co-treatment of Fulvestrant in combination with estrogens. Using this phenotypic readout, the E-Morph Assay measures the estrogenic or anti-estrogenic activity of test substances in 96- or 384 well plate format. Since the functional effects are also key to metastatic cancer progression, this novel endpoint may also be used in characterizing tumor progression and metastatic condition in patients.

COMMERCIAL OPPORTUNITY

The E-Morph Assay is the first test method that leverages the potential of high-content imaging and machine learning approaches to determine estrogenic activity based on morphological changes in a quantitative manner. It further integrates readouts to monitor cell viability and detect cytotoxicity, which is not always considered in other cell-based assays. The possibility to screen for both estrogenic and anti-estrogenic effects of test substances using the same readout illustrates the versatility of this assay. The E-Morph Assay is useful for efficient analysis of comprehensive substance libraries in order to prioritize substances, thereby avoiding unnecessary animal testing.

20 YEARS BfR German Federal Institute for Risk Assessment

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The technology is open for licensing, further co-development is highly welcomed.

DEVELOPMENT STATUS

The applicability of the E-Morph Assay for automated HTS approaches has been demonstrated using a reference substance library comprising 440 toxicologically-relevant industrial chemicals, biocides, and plant protection products in order to identify novel substances with estrogenic activities. The screening identified 'known' estrogenic substances with potencies correlating very well with published data. Current work on the further development of the E-Morph Assay include its adaptation to serum-free/defined cell culture conditions, its implementation at other partner site screening units to demonstrate its transferability, and its application for screening larger substance libraries comprising thousands of natural and drug-like compounds.

PATENT SITUATION

Patents are pending in EP and US (priority of January 2018), with notice of intention to grant in EP.

FURTHER READING

Klutzny et al. (2022), Environ. Int. 158:106947; Kornhuber et al. (2021), Environ. Int. 149:106411; Bischoff et al. (2020), iScience 23:101683

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