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SCREENED: A Multistage Model of Thyroid Gland Function for Screening Endocrine-Disrupting Chemicals in a Biologically Sex-Specific Manner

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Abstract:

Endocrine disruptors (EDs) are chemicals that contribute to health problems by interfering with the physiological production and target e_ects of hormones, with proven impacts on a number of endocrine systems including the thyroid gland. Exposure to EDs has also been associated with impairment of the reproductive system and incidence in occurrence of obesity, type 2 diabetes, and cardiovascular diseases during ageing. SCREENED aims at developing in vitro assays based on rodent and human thyroid cells organized in three di_erent three-dimensional (3D) constructs. Due to di_erent levels of anatomical complexity, each of these constructs has the potential to increasingly mimic the structure and function of the native thyroid gland, ultimately achieving relevant features of its 3D organization including: (1) a 3D organoid based on stem cell-derived thyrocytes, (2) a 3D organoid based on a decellularized thyroid lobe stromal matrix repopulated with stem cell-derived thyrocytes, and (3) a bioprinted organoid based on stem cell-derived thyrocytes able to mimic the spatial and geometrical features of a native thyroid gland. These 3D constructs will be hosted in a modular microbioreactor equipped with innovative sensing technology and enabling precise control of cell culture conditions. New superparamagnetic biocompatible and biomimetic particles will be used to produce "magnetic cells" to support precise spatiotemporal homing of the cells in the 3D decellularized and bioprinted constructs. Finally, these 3D constructs will be used to screen the e_ect of EDs on the thyroid function in a unique biological sex-specific manner. Their performance will be assessed individually, in comparison with each other, and against in vivo studies. The resulting 3D assays are expected to yield responses to low doses of di_erent EDs, with sensitivity and specificity higher than that of classical 2D in vitro assays and animal models. Supporting the "Adverse Outcome Pathway" concept, proteogenomic analysis and biological computational modelling of the underlying mode of action of the tested EDs will be pursued to gain a mechanistic understanding of the chain of events from exposure to adverse toxic e_ects on thyroid function. For future uptake, SCREENED will engage discussion with relevant stakeholder groups, including regulatory bodies and industry, to ensure that the assays will fit with purposes of ED safety assessment. In this project review, we will briefly discuss the current state of the art in cellular assays of EDs and how our project aims at further advancing the field of cellular assays for EDs interfering with the thyroid gland.

Keywords: endocrine disruptors, in vitro models, bioprinting, omics, decellularization, organoids