第 4 回日本生殖発生毒性フォーラム「話題提供」

株式会社新日本科学グループ
Ina Research Inc.

Implementation of New Alternative Methods into regulated toxicology assays.

-Increasing predictivity of compound teratogenicity and endocrine disruption through the zebrafish model.-

Carles Cornet Bartolomé, PhD
ZeClinics, Head of Toxicology Area

２０２２年１１月１２日（土）

放送予定：**16:00～17:00**

会場： Web 開催（Zoom）

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Powering discovery with Zebrafish

Biography:

Carles Cornet is an expert in zebrafish biology and drug discovery.
He joined ZeClinics team in 2015 as a PhD student, where he has optimized the use of the zebrafish model as a novel tool to assess drug safety and antitumoral efficacy. In January 2020, year in which he obtained his PhD in Biomedicine from the Pompeu Fabra University in Barcelona, Carles became a project manager of the company, involved inside the toxicology and oncology areas, as well as in the CNS behavioral efficacy area. Since July 2022 he has become the Head of the Toxicology Area.

Abstract:

Acute and long-term exposure to environmental chemicals is a risk not only for the environment but also for human health. Exposure to chemicals during embryonic development may result in drastic effects ranging from abnormal growth of anatomical structures to lifelong mental disabilities. Furthermore, humans are also at risk at their adulthood as growing evidence suggests that alterations of the endocrine system induced by the exposure to such environmental chemicals severely compromise human health. The establishment of rapid, reliable and cost-effective methodologies for detecting developmental toxicity of chemical substances, as well as the so-called endocrine-disrupting (ED) compounds and the effects associated with their exposure,is a pressing need for both the scientific community and regulatory agencies.

In the era of the 3Rs principles implementation there is a strong interesting in the seek for new experimental methods to reduce animal testing. Small fish like zebrafish has proven an excellent experimental system and suitable alternative model to animal testing because of the large degree of conservation with higher vertebrates. Additionally, zebrafish have several experimental advantages, namely ex utero rapid development, embryo transparency, and large progenies. All these make zebrafish a competitive model for high-throughput screening of potential teratogenic and ED compounds in a fast and cost-effective manner.

Here, we will present the last developments on the use of zebrafish larvae in predicting teratogenic and ED compounds in humans. In a first section, we will present the establishment of an innovative automated high-throughput screening platform for teratogenic drugs. The platform was validated by testing on zebrafish larvae a library of 31 known compounds classified as teratogens and non-teratogens in mammals and by assessing 16 phenotypical parameters related to embryo development. Our results show a high correlation with humans: 87.50% sensitivity, 81.82% specificity and 74.19% accuracy, increasing the prediction level reported in rodents. Importantly, based on the results obtained in this validation study, we have developed a deep learning algorithm, able to discriminate all the defined phenotypic parameters, sort larvae as positive or negative for qualitative phenotypes and extract values from quantitative ones. In a second section, we will present a robust high-throughput assay to detect potential ED compounds. Changes at the transcriptomic level (messenger RNA content, mRNA) have been identified as biomarkers of ED exposure. In this study, we exposed embryonic zebrafish to the natural ligands 17 β-estradiol, testosterone, and 3,3',5-triiodo-L-thyronine (T3), and identified eight genes representing the three major endocrine axes – estrogenic, androgenic and thyroid. The identified genes were subsequently validated using six previously reported ED compounds. The results obtained pave the way for the integration of zebrafish in novel regulatory guidance documents as a reliable alternative model for the improvement of human teratogenicity and ED compounds prediction.

-Keywords: **zebrafish, endocrine disruption, Developmental toxicity, Artificial intelligence, NAMs**