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Abstracts

Screening of multi-endocrine disruptors in zebrafish

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Small fish like zebrafish (*Danio rerio*) are an excellent alternative to *in vitro* and *in vivo* model. They offer a unique experimental system where screening assays can be performed at the whole animal level, being at the same time compatible with the 3R principles (replacement, reduction and refinement in animal testing).

The zebrafish is currently used as a model for the evaluation of acute and developmental toxicity and for the screening and testing of potential thyroid (TD) and endocrine disrupters (EDCs), as described in the OECD Guidelines. Endocrine disruptors (EDCs) are chemicals that by interfering with the endocrine system can have an adverse effect at the developmental, neurological, immune and reproductive levels. Thyroid Disrupting (TD) compounds specifically alter the function of thyroid gland through the interference with the synthesis, transport and/or binding of the thyroid hormones. The negative impact of EDCs is becoming a real public health issue, therefore the necessity of tests to assess the potential risk of new chemicals before they are marketed is increasing. With the purpose of expanding the number of tests available to identify estrogenic, androgenic and TD substances, we evaluate gene expression of 7 biomarkers in 5 dpf zebrafish larvae exposed for 3 days, starting at 2dpf. In three out of 10 EDCs selected compounds (genistein, testosterone and nandrolone) and in 1 out of 9 TD selected substances (bisphenol A), no changes in biomarkers gene expression were detected. This screening methodology showed a sensitivity of 82.6 % and a specificity of 100%. An alternative screening method for TD substances assessment was developed using the Tg(tg:mcherry) transgenic zebrafish line. The fluorescence of the reporter gene allows monitoring in vivo the upregulation of the thyroglobulin gene expression as a compensatory reaction to thyroid gland disruption. transgenic embryos were exposed to the test substances from 48 to 120 hpf (hours post-fertilization) and subsequently imaged by fluorescence microscopy. A dose-dependent increase of the fluorescence was observed for 7 out of 9 TD substances showing a sensitivity of 80 % and a specificity of 100%. The intensity values were fitted to a concentration-response regression model to calculate TD predictors, such as the Benchmark Concentration (BMC), Thyroid Disrupting Index (TDI), and Relative TD Potency (RTP).

This screening methodology showed to be a sensitive and cost-effective assay to evaluate and identify potential EDCs and TD chemicals.

In vitro biotransformation of proteratogens in different laboratory animal models, including the zebrafish

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The zebrafish is a vertebrate belonging to the Cyprinidae family and shares several physiological, morphological, and histological similarities with mammals including common characteristics in developmental biology. This makes the zebrafish embryo model an interesting alternative in developmental toxicology which, until now, mainly relies on *in vivo* models (rodents and non-rodents). Although the metabolic capacity of mammalian models has already been thoroughly investigated, there is still a knowledge gap for the zebrafish model. Above all, the biotransformation capacity of zebrafish embryos remains a point of debate. This is critical for proteratogens that require bioactivation to exert their teratogenic potential during organogenesis. Bioactivation is mainly performed by cytochrome P450 families 1 to 3 and their gene expression and activity is low in zebrafish up to 3 days post fertilization [1]. The overall aim of this study is to investigate whether selected mammalian proteratogens are metabolized by zebrafish, and if so, to compare their metabolite profile with the one generated in man, rat and rabbit, as the latter two species are commonly used in developmental toxicity studies. We selected three known mammalian proteratogens (carbamazepine, phenytoin and tegafur) that have already been investigated in developmental toxicity screening in zebrafish embryos [2]. Each substrate is exposed to adult wild type AB zebrafish, Sprague Dawley rat, New Zealand White rabbit and human (positive control) liver microsomes (200 µg/ml) for 0, 60, 120 and 180 minutes at 28.5°C in 100 mM KH_2PO_4/K_2HPO4 buffer, pH 7.4, and NADPH regenerating system reagents A (5%) and B (1%). A concentration range (0.1-10 µM) is used for each substrate. The reaction is stopped by adding cold acetonitrile (4°C) containing 0.39 µM of lamotrigine, the internal standard. Quantitative depletion of the substrate is investigated by UPLC – Triple Quadrupole MS analysis (ACQUITY UPLC-TQ detector, Waters, Milford USA). As such, the *in vitro* metabolic rate can be compared for the investigated species. Further qualitative investigation will be performed to identify the metabolites that are produced by zebrafish for the selected mammalian proteratogens. These data can be very useful when using the zebrafish embryo for safety assessment of drugs in development and bring more insight into the potential biotransformation capacity of this increasingly used model.

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Assessment of neurodevelopmental adverse effects induced by Intra-uterine growth restriction and testing of future therapies. Application in an in vitro rabbit neurosphere model.

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Introduction: Intrauterine growth restriction (IUGR) is defined as a significant reduction of fetal growth rate leading to a birth weight below the 10th percentile for the corresponding gestational age. The prevalence accounts for 5-10% of all pregnancies, approximately 600.000 cases in Europe. Placental insufficiency reduces placentary blood flow leading to fetal development under chronic hypoxia which is associated to neurodevelopmental damage, cognitive dysfunctions and cardiovascular adverse outcomes [1]. The characterization of neurostructural changes in fetus with IUGR is essential to design therapeutic strategies directed to limit ist deleterious effects.

Methods: The induction of IUGR was performed in one of the uterine horns of pregnant rabbits at gestational day 25 (GD25). Neurospheres were obtained from the whole brain of IUGR and normal grown rabbit pups immediately after caesarean delivery at GD30.
For the establishment of the neurosphere culture the ability to mimic basic processes of brain development was evaluated, including proliferation, migration, differentiation, synaptogenesis and cellular viability [2,3]. To find a neuroprotective therapy preventing/reversing adverse effects of IUGR six different compounds at increasing concentrations (Docosahexaenoic acid (DHA), choline, lactoferrin, melatonin, zinc, and 3,3′,5-Triiodo-L-thyronine (T3)) were tested.
Basic processes of neurogenesis were assessed to determine the maximum tolerated concentration (MTC) and the effective concentration (EC). Criteria to define the MTC encompasses a viability >70%, a not significantly reduced migration distance or oligodendrocyte percentage compared to the vehicle control.

Results: We have established for
the very first time an in vitro model based on primary rabbit neuronal progenitor cells (NPCs) cultured as three-dimensional cell aggregates called neurospheres, which are able to proliferate, migrate and differentiate into neurons, oligodendrocytes and astrocytes. We successfully developed new endpoints like neurite outgrowth, branching and synaptogenesis. By comparing the functionality of control and IUGR neurospheres we identified that rabbit NPCs from IUGR individuals have a significantly reduced ability to form oligodendrocytes. DHA (MTC=10µM;EC=1µM), melatonin (MTC=3µM; EC=1µM) and T3 (MTC=30nM; EC=0,1nM) have been selected as the most promising therapies due to their promoting effects on oligodendrogenesis.

Conclusion: The established in vitro model allows us to evaluate different processes of neurogenesis in a fast, economic and ethic way and contributes to a better understanding of IUGR induced neurodevelopmental damage and to the selection of new neuroprotective therapies.

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A new guide to diagnose thalidomide embryopathy in Japan

Hinoshita[1] Fumihiko, Kayamori[2] Ryoji and the research group[3] on grasping the health and living situation as well as creating the support infrastructure for thalidomide-impaired people in Japan*

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[Introduction] About 60 years have passed since thousands of babies, exposed in utero to thalidomide, were born with a variety of visceral disorders and birth defects such as limb deformities, phocomelia, and hearing loss or impairment. However, some specific problems remain unresolved, including new claimers for thalidomide embryopathy (TE). Many persons with congenital birth defects have newly claimed to be thalidomiders in European countries as well as in Japan, and a UK group showed a diagnostic algorithm for TE (DATE) in 2019 [1]. Therefore, we also felt the necessity to determine new diagnostic criteria characteristic to Japan.

[Methods] Six members were selected for the diagnostic criteria development committee of TE from the members of the Official Research Group in Japan. The committee consisted of the research group head, 2 rehabilitation doctors, a radiologist, an otorhinolaryngologist and an ophthalmologist. The committee met several times in 2019 to establish a guide to diagnose TE based on objective references and past experiences as well as on radiological findings, with reference to DATE.

[Results] After arduous discussion, we have determined the new diagnostic guide to diagnose TE in Japan as follows:

- Definitive case is one which satisfies all of the following conditions: born in the years between 1958 and 1964; demonstrated mother took thalidomide during pregnancy; children having bilateral congenital and typical limb deficits, or congenital hearing impairment, or both.
- Suspected case, which must be carefully evaluated by the diagnosis committee, with the following conditions: basically born in the years between 1958 and 1969; mother lived in the countries where thalidomide-containing drugs were sold; no family history of similar birth defects; having at least one of the congenital problems specific to TE, such as deformities of the upper limb, the lower limb, face, eyes or ears as well as hearing impairment; upper limb deformity is bilateral, not unilateral.

Major TE-specific findings should be identified especially in the suspected cases by the diagnosis committee of the official research group. Major TE-specific findings will also be discussed.

[Conclusion] We have developed a new diagnostic guide for new claimers to diagnose TE in Japan.

Reference

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A Clinical Review and Introduction of the Diagnostic Algorithm for Thalidomide Embryopathy

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Evaluation coding: from 1 to 5 (been 5 the highest)

- Scientific content: 2x
- Teratogenic applicability:
- 2020 ETS symposiums´ them:

ZNF48 and ZNF84 are potentially involved in the regulation of genes affected by thalidomide

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Introduction: Thalidomide's ability to degrade zinc finger transcription factors (TFs) with a C2H2 protein domain occurs through Cereblon binding (Thal-CRBN). These neosubstrates might be the missing link to the understanding of Thalidomide Embryopathy (TE) molecular mechanisms. However, it is not totally understood how this property and the previously known ones (anti-angiogenesis and immunomodulation) interact. This study aims to evaluate whether C2H2 Thal-CRBN neosubstrates could be TFs of proteins already known be affected by thalidomide.

Methods: Proteins affected by thalidomide were obtained through literature review, comprising only experimental studies in human embryonic cells and evaluation of syndromes phenotypically similar to TE. From this review, we assembled a protein-protein interaction network, in order to obtain the main proteins for each property. The C2H2 neosubstrates were obtained from an experimental assay [1], considering only the significantly degraded ($p<0.05$). Data for Thal-CRBN and the analogues lenalidomide (Len-CRBN) and pomalidomide (Pom-CRBN) were included. The genes regulated by the TFs were accessed through TF2DNA database. Statistics was performed in R v.3.6.2 *igraph* package.

Results: Seventy-one proteins were obtained through literature review. After systems biology analyses, a network was generated comprising the proteins affected by thalidomide. Based on network statistics analyses, the proteins CDH5 and NOS3 were selected for anti-angiogenesis, CUL4A and CRBN for Cereblon binding property, FGFR1 for limb development, GSK3B, MAPK8, and NFKB1 for oxidative stress, CYP2C19 for metabolism, TNF for immunomodulation, and CTNNB1 as the network central element. Proteins TBX5, SALL4, ESCO2, RECQL4, and RBM8A, which cause genetic syndromes from which TE is a phenocopy, were also selected. Sievers study demonstrated 415 TFs affected by Thal-CRBN, Len-CRBN, and Pom-CRBN with statistical significance, being 67 degraded by all the three drugs, whilst the others were affected by one or two of these drugs. According to TF2DNA, 35/415 TFs acted as regulators of the expression for the protein coding genes selected with network analysis. ZNF48 had the biggest number of proteins, five, being: CTNNB1, FGFR1, NOS3, RBM8A, and SALL4. Protein FGFR1 is regulated by the biggest number of TFs, eleven, including ZNF48 and ZNF84. The latter is the only of the 35 degraded by all the three drugs.

Conclusions: We identified two TFs, ZNF48 and ZNF84, as potential neosubstrates of the Thal-CRBN binding. It is known ZNF48 and ZNF84 are zinc finger TFs, however there are no further information about their function or pathways they are involved with. ZNF84 has been statistically associated to human embryonic stem-cell signature, but no other research has been conducted. More studies in those TFs are needed in order to understand their effect on the known-affected protein and how these degraded neosubstrates could be connected to thalidomide previously known properties.

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Challenges when designing juvenile animal studies that meet global regulatory expectations

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Compound X is intended to be used world-wide as an anti-infective in adult and pediatric patients. The nonclinical pediatric strategy was designed to support treatment in the pediatric population including newborns, infants and children. Two juvenile animal studies (JAS) were performed following requests from the EMA and FDA. In JAS1, oral administration was initiated in rats on postnatal day (PND)14 whereas in JAS2 dosing started on PND4. The animals in both studies were dosed up to PND56. Endpoints were identical including in-life observations, body weight, food intake, physical and sexual development, clinical pathology, anatomic pathology, neurobehavioral testing, and toxicokinetic assessments. The age at dosing initiation in study 1 was triggered by effects on the kidney observed in adult repeated dose toxicity studies and took into account the immature state of the rat kidney versus the human (morphological development important till PND14-15 in rat but complete prenatally in humans); furthermore, it complied with a specific request from the EMA. Subsequently, the age of PND14 at dosing initiation was not acceptable for the FDA and a JAS2 had to be performed with dosing starting on PND4 to also assess potential effects on other developing organs during the early postnatal development period. Overall, in both studies, treatment was well tolerated and did not induce effects associated with systemic toxicity. There were non-adverse changes in clinical pathology parameters and no gross or microscopic findings in JAS1. Renal tubular changes were seen at the end of the treatment period in the high dose group of JAS2. These changes were considered non-adverse and recovered after a 4-week treatment-free period. In conclusion, the findings in both studies were similar which resulted in the same NOAEL. This case illustrates the challenges when designing a JAS that is acceptable and meets global regulatory expectations. The new ICH S11 guideline[1] provides more clarity and alignment on the need and design of a JAS, thus avoiding unnecessary studies and use of animals.

Ref 1: ICH Guideline S11 on Nonclinical Safety Testing in Support of Development of Paediatric Pharmaceuticls. ICH step 5 reached, April 2020.

BDRP AND EUROPEAN TERATOLOGY SOCIETY EXCHANGE LECTURE

As the Society of Birth Defects Research and Prevention (BDRP) reaches its 60th anniversary, we find ourselves both memorializing its roots with nostalgia and exploring its future with eager anticipation. In the 1960s, the scientific leaders in the field of teratology proposed a number of basic principles that have been an accepted foundation for basic research, regulatory testing, risk decisions, environmental management, and clinical application. The annual Exchange Lecture this year explores one of the important early tenets, Karnofsky's Law, which states that any drug administered at the proper dosage, and at the proper stage of development to embryos of the proper species will be effective in causing disturbances in embryonic development. Speakers from BDRP and the European Teratology Society (ETS) will delve into the time-honored validity of this law, its historical contribution, and its relevance to the future of developmental toxicology assessment and decision making for pharmaceuticals and chemicals. Is Karnofsky's Law still alive and well in current practice, or has it outlived its relevance?

Intrauterine growth restriction: clinical consequences on health and disease at adulthood

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Intrauterine growth restriction (IUGR) affects 10 to 15% of all pregnancies worldwide. IUGR may result from maternal, placental or fetal origin. Maternal malnutrition before and during pregnancy represents the most prevalent non-genetic or placental cause. IUGR reflects an abnormal adaptive fetal growth in a deleterious environment. This first hit deeply alters the developmental programming of many organ systems. Individuals born after IUGR are more susceptible to develop diseases related to subsequent stressors through a lifetime. Animal models help to decipher the underlying causes of dysregulated pathways and molecular modifications conditioning health and disease in adult offspring born after IUGR. The aim of this review is to summarize current knowledge on long term consequences of IUGR, integrating animal models and human studies for a better care of IUGR-born individuals in a life course perspective.

Neurodevelopmental outcomes of fetal growth restriction

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Poor fetal growth affects a significant proportion of pregnancies worldwide. Preterm birth is more frequent in pregnancies with fetal growth retardation (FGR) than in pregnancies with normal fetal growth. Fetal growth retardation can result from a heterogeneous set of underlying aetiologies and clinical characteristics. It has been associated with impaired neurodevelopmental outcome, affecting multiple developmental domains,

Overall, there is considerable heterogeneity in existing studies that investigate long term neurodevelopmental outomes of FGR. For example, there are inconsistent definitions of growth restriction, time of onset of FGR, inclusion and exclusion criteria, and outcome measures, all of which makes comparison between studies difficult. Existing evidence overall suggests that, at school age, the risk for severe neuromotor impairment (Cerbral Palsy, CP) is higher in term born children with FGR, whereas general cognitive abilities are not significantly different to their peers without FGR. However, there is an indication that attentional abilities, which are important for a child's learning and behavior as they progress through school, are an area in which those with a history of FGR are at risk for difficulties. In contrast, in children born preterm, FGR does not appear to pose a higher risk for CP, but preterm children with FGR are at significantly higher risk of impairment of general cognitive abilities, and, in particular, memory, executive function, and communication skills may be affected. However, it is often difficult to disentangle the effects of FGR from those of preterm birth per se. It is important to follow up children with FGR, both those born preterm born at term, into the school age years because more subtle, but nevertheless relevant, difficulties may take time to emerge, and may be more visible in the more demanding school environment.

Placental phenotypes in fetal growth restriction: Lessons from experimental animals

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Fetal growth restriction (FGR) affects ≈5-7% of human pregnancies in developed societies and has immediate and life-long consequences for child health. Although the pathogenesis of FGR is considered to be multifactorial, placental insufficiency, defined as the inability of the placenta to provide nutrients according to fetal demands, is recognised as a main cause of FGR in the develop world. Despite this, the mechanisms underlying the development of placental insufficiency and FGR are not yet well defined. In this scenario, the use of mammalian models provides an opportunity to improve our knowledge. Laboratory species like rodents (eg. mice or guinea pigs) and rabbits have haemochorial placentation and share some similarities in fetal development to humans. Moreover, in these laboratory species, we have the tools to successfully modify their environment (eg. nutrition), their genome (eg. knock-in, knock-down/out in mice), as well as perform scanning and surgical procedures to study feto-placental physiology during gestation. During this talk, we will describe the availability and knowledge gained from employing different animal models, with a focus on small animal species when studying the pathogenesis of FGR. Specifically, we will explore: (*1*) the contribution of maternal nutrition in feto-placental growth by studying the undernourished pregnant rabbit model [1], (*2*) the importance of an adequate utero-placental blood flow for fetal development by using progressive uterine artery occlusion in the pregnant guinea pigs [2], and (*3*) the significance of metabolic signalling proteins, namely phosphoinositide 3-kinase p110α, in regulating placental nutrient supply and fetal growth using genetic manipulations in mice [3]. Overall, we hope to engage and inspire investigators to employ animal models in their research so we can improve our knowledge on placental physiology and in the future, identify the mechanisms underlying FGR and treatment strategies.

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