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New Diagnostic and Therapeutic Tools against Multidrug-Resistant Tumours

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WG 1 – WG 4

Abstract Book

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WG 4

Evaluation of anticancer compounds activity and toxicity in zebrafish model

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Zebrafish (*Danio rerio*) is an excellent model for studying toxicity and biological activities of novel compounds with anticancer potential. This model is widely utilized in biological research as it is comparable to human counterpart both molecularly and pathologically. As an *in vivo* system for toxicology, zebrafish has numerous advantages such as rapid and *ex utero* development, transparent embryos in early stages, high fecundity allowing high-throughput screening and cost effectiveness. Furthermore, evaluation of known toxic compounds in zebrafish revealed 63–100% predictability making zebrafish a very useful tool for studying toxic effects [1, 2]. In addition, embryonic zebrafish cancer models can be used for studying pathways and processes relevant to human malignancy including tumor-induced angiogenesis, tumor invasiveness, proliferation and migration. These models can be generated using transgenesis, gene inactivation, xenotransplantation, and cancerogenic induction. Herein, we present the results obtained in zebrafish toxicity studies of siramesine, a sigma receptor agonist with anticancer potential. Concentration dependent increase in lethality, induced by siramesine treatment, was observed in zebrafish embryos at 24 h post fertilization (hpf), 48 hpf and 72 hpf. Various concentration dependent toxic effects on embryo development were also observed, as well as decreased hatching rate in embryos treated with 5 μM and 10 μM siramesine at 72 hpf. Results obtained in zebrafish cancer model generated via xenotransplantation are also presented. This model was utilized to study the effect of Src tyrosine kinase inhibitor pro-LDS10 on the invasiveness of microinjected human glioblastoma cell line U87. Treatment with 5 μM pro-LDS10 resulted in significant reduction of U87 migratory potential at 4 days post injection.

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In vitro and *in vivo* approaches for non-clinical safety assessment: emphasis on hepatotoxicity

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Liver toxicity is one of the leading cause of drug withdrawals from the market. Iproniazid (monoamine oxidase inhibitor), troglitazone (anti-diabetic drug), and bromfenac and Benoxaprofen (non-steroid anti-inflammatory drug, NSAID) are in the long list of drugs, withdrawn from the market, because of idiosyncratic liver injury. However, at present liver safety does not form part of the core battery of pre-clinical tests required for initial safety pharmacology from regulatory bodies. EMEA have published draft guidance on the non-clinical assessment of hepatotoxic potential, but no regulations are set in place yet. Currently, liver toxicity screening during both the pre-clinical in vitro and in vivo testing and clinical phases of the development process forms the basis of hepatic safety testing. Here, we present some methodologies applicable to the early assessment of potential intrinsic hepatotoxicity of new drug molecules. The presentation will focus on *in vitro* and *in vivo* methods for evaluation of liver toxicity of newly developed nano-sized drug-delivery systems. An important goal of research into this field is to establish adequate *in vitro* / *in vivo* models that are valid and able to predict drug induced liver toxicity during lead optimization, before any hepatotoxic molecule under development unnecessarily progresses into clinical studies.