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## Translational Biology using the Zebrafish Model Organism

The zebrafish, *Danio rerio*, is becoming an increasingly important experimental organism and significant advances have recently been made in the use of zebrafish for the modelling of human diseases. Zebrafish share significant behavioural, physiological and pharmacological similarities with humans and a large body of evidence is accumulating showing that zebrafish can accurately represent human biology. The genome has been largely sequenced and a variety of tools are available for gene knockdown, making target validation in zebrafish models of disease viable. The larvae are transparent, which enables visualisation of organs; they are tolerant of DMSO up to 2%; they can absorb compounds directly through their skin and can live in ~100 microlitres of water. Therefore, it has been possible to establish medium-throughput, high-content assays for screening in 96-well plates using small amounts of compound, which can facilitate *in vivo* testing of compounds at a much earlier stage of the drug discovery process than has previously been possible. Assays can be formatted to test compounds for efficacy in a particular organ system or, conversely, to evaluate safety pharmacology or liability potential of compounds, for example, embryo toxicity or cardiotoxicity.

Ophthalmology is an area where the zebrafish approach may be particularly advantageous. Zebrafish have rich colour vision and a high similarity in retinal physiology and pathology to humans. Methodologies for the assessment of visual function in zebrafish, i.e. optomotor and optokinetic responses (OMR and OKR), have been developed and validated using drugs which are known to have adverse ophthalmic effects in man. In contrast, these assays measuring OMR and OKR may be used in models of retinal degeneration to address areas of high unmet medical need such as age-related macular degeneration. In addition, a variety of CNS disorders can be modelled in zebrafish and the validation of a zebrafish model of epilepsy will be described. An understanding of the blood brain barrier in zebrafish and the penetration of test compounds into the CNS is important for the interpretation of results in neurobehavioural assays: Studies have been performed to ascertain the time-course of the formation of the blood brain barrier in zebrafish larvae. Finally, the establishment of therapeutic windows is important for anti-epileptic drugs and an illustration of using zebrafish models for assessing both anti-epileptic activity and cardiotoxicity will be given.