

Abstract:

The zebrafish offers many compelling advantages for drug discovery, including for high throughput screening (HTS). The high genetic and physiological homology to higher vertebrates such as mammals increases the probability that molecules bioactive in the zebrafish would be clinically relevant. The small dimensions and ease of breeding and care renders the zebrafish practical and economical for HTS in plates of 96-wells or even more. We have utilized these useful properties of the zebrafish to investigate the effects of radiation and radiomodifiers on zebrafish embryonic survival, and have demonstrated that radiation has effects in zebrafish similar to that seen in humans. We have also found that radiation results in caspase activation in embryos that is detectable via proluminescent probes, with resultant signal proportional to the degree of end-organ damage. This assay can be performed in 96-well microplates, both positive and negative controls are available, requires only the addition of reagents followed by minimal subsequent manipulation, and results in signal proportional to the radiation dose and of high signal-to-background ratio all properties useful for HTS. This application proposes to capitalize on our preliminary and published findings to discover, via HTS, molecules that either protect against the deleterious effects of, or increases the lethal efficacy of ionizing radiation. The discovery of radiomodifying molecules that reduce caspase activation may lead to agents useful for reducing the complications and side effects of therapeutic anticancer radiation therapy or acts of bioterrorism. Alternatively, molecules that exacerbate caspase activation may be further investigated for antitumor properties as novel therapeutic agents.