NEW TOXICITY ASSAYS IN THE CURRENT DRUG DEVELOPMENT PROCESS – THE ZEBRAFISH MODEL BRIDGING THE GAP BETWEEN *IN VITRO* AND *IN VIVO* RESEARCHES

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Developing a new drug through preclinical research, whether it is a new chemical entity or a biologic therapeutic, is a very complex and long process, which can take many years with a lot of uncertainty on its success. One of the fundamental challenges in this process is the discovery of effective molecules, understanding their mechanism of action inside a living organism, as well as potential toxic effects, which are traditionally tested *in vitro* and *in vivo*. *In vitro* or cell culture systems cannot recapitulate an entire organism. On the other hand, animal studies are not suitable for high-throughput screening and experience many difficulties. Therefore, introducing the zebrafish model (*Danio rerio*) into preclinical trials is a way to make drug development more efficient and financially viable, simplifying their path to clinical trials, while reducing failures in the later stages of this process. The zebrafish model has emerged as a promising biotechnological platform for this purpose, due to its high molecular-genetic, physiological and immunological similarity with mammals, including humans. Attractive characteristics such as small size and optical transparency of embryos and existence of various transgenic lines with fluorescently labelled cells, tissues or organs make them adequate experimental model for biomedical researches. Moreover, following 3Rs principles (replacement, reduction and refinement) for more ethical use of animals, the zebrafish is regarded as a valid alternative to mammalian animals for toxicity testing.

NOVI TESTOVI TOKSIČNOSTI U OTKRIĆU I RAZVOJU LEKOVA – MODEL ZEBRICE KAO MOST IZMEĐU *IN VITRO* I *IN VIVO* ISPITIVANJA

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Razvoj novog leka kroz pretklinička ispitivanja, bilo da se radi o novoj hemijskoj supstanci ili biološkom leku, je veoma složen proces, koji može da potraje mnogo godina, sa dosta neizvesnosti u pozitivan ishod. Jedan od fundamentalnih izazova u ovom procesu je otkrivanje efikasnih molekula, razumevanje njihovog mehanizma delovanja unutar živog organizma, kao i potencijalnih toksičnih efekata, koji se tradicionalno ispituju *in vitro* i *in vivo*. *In vitro* sistemi ili ćelijske kulture ne mogu reprezentovati ceo organizam. S druge strane, *in vivo* studije na eksperimentalnim životinjama nisu pogodne za „*high-throughput*" skrining i imaju mnogo nedostataka. Stoga, uvođenje modela zebrice (*Danio rerio*) u pretklinička ispitivanja predstavlja način da se razvoj lekova učini efikasnijim i finansijski pogodnijim, pojednostavljujući njihov put do kliničkih ispitivanja, uz smanjenje neuspeha u kasnijim fazama ovog procesa. Model zebrice se pojavio kao obećavajuća biotehnološka platforma za ovu svrhu, zbog visoke molekularno-genetske, fiziološke i imunološke sličnosti sa sisarima, uključujući i ljude. Atraktivne karakteristike kao što su mala veličina i optička transparentnost embriona i postojanje različitih transgenih linija sa fluorescentno obeleženim ćelijama, tkivima ili organima čine ih pogodnim eksperimentalnim modelom za biomedicinska istraživanja. Štaviše, prateći 3Rs principe (zamena, smanjenje, usavršavanje) za dobrobit eksperimentalnih životinja, zebrica se smatra validnim alternativnim modelom za ispitivanje toksičnosti.