LRI-AIMT5.2

A developmental ontology-based computational model for mammalian neural tube closure for *in silico* prediction of compound-induced neural tube defects.

Summary

The aim of this study was to build a map of the cellular processes and their interactions underlying the closure of the neural tube in vertebrates, and to translate this map into a computational model that can be used as a tool to predict the effects of chemicals on neural tube closure. In the process of neural tube closure, cellular behavior is governed by specific gene expression patterns, that drive cell proliferation, differentiation and interactions in a spatially strictly defined matter. In the neural plate stage, six cell types were defined with their specific gene expressions, the cytokines they produce and the cell behaviors they influence. The resulting map is a complete mechanistic description of the biology underlying neural tube closure. In parallel, a 3D computational model was developed describing the elevation of the neural plate to a semi-tube. The full closure could not yet be modelled within the time frame of the project. This was caused by the realization during the project that the anticipated 2D closure model would neglect some essential features of neural tube closure. The 3D approach that was then followed was logically of a much higher complexity and therefore required more computing time than available within the project.

The next step will be the completion of the computational model, followed by functionally linking the computational model with the biological map, so that the computational process is virtually governed by the biological mechanisms. Once that has been achieved, it will be possible to feed data from compound-induced gene expression changes observed in simple in vitro cell systems into the computational model, which will then predict effects at the level of neural tube formation. Thus, the combination of simple in vitro assays with the computational model that integrates data at the level of the embryo will provide an animal-free approach to chemical hazard assessment.

It is expected that computational approaches supported by in vitro assays will increasingly be used for chemical hazard assessment. It offers opportunities to avoid animal testing, to fine-tune hazard assessment to human physiology, and allow for mechanistic understanding of chemical toxicity, providing a better informed basis for risk assessment.