Healthcare industry BW

Stem-cell tests to provide protection to unborn babies

The development of unborn babies may already be impaired in the womb by pollutants from the environment, food and drugs to which their mothers are exposed. Reliable and informative toxicity tests are necessary in order to assess and prevent the effects toxic substances may have on unborn babies. The limited reliability of animal tests for assessing potential risks is well known, not least since the thalidomide scandal in the 1960s, which is why many hopes are pinned on human cell culture systems. Biologist Dr. Tanja Waldmann from Konstanz University is developing toxicity test systems based on human embryonic stem cells, which contribute to improved consumer protection and also cut down on the number of animals that need to be sacrificed.

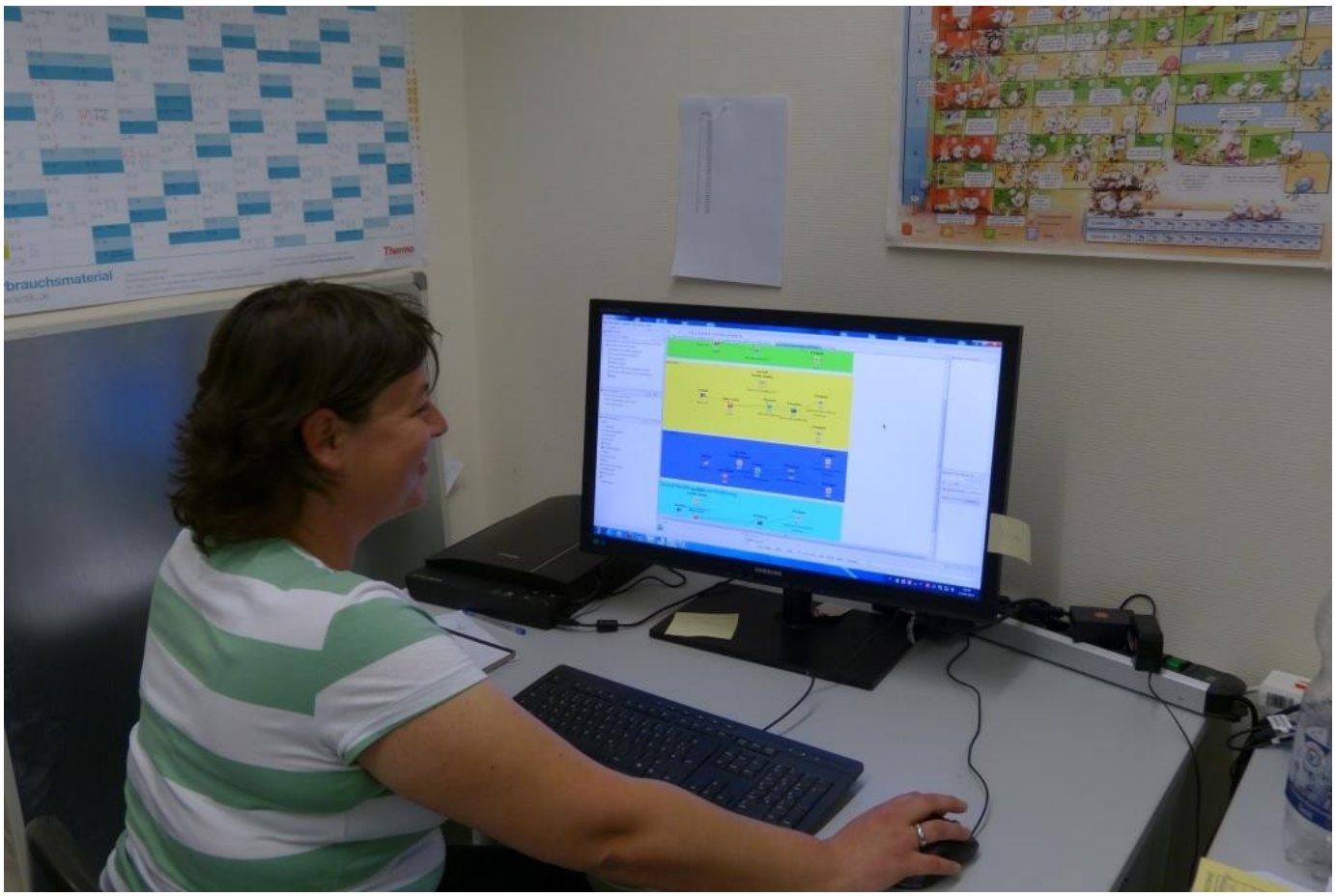
Dr. Tanja Waldmann (right) and her doctoral student Nina Balmer are developing cell culture systems with human embryonic stem cells.

Although labels on wine bottles and packaging inserts with health warnings for pregnant women are standard procedure, clear data on the potential health risks of many substances we encounter in our everyday life are still lacking due to the fact that the study of chronic exposure to low doses in animals is difficult and in people only possible post-mortem. Even though the risks may not lead to major malformations, small modifications can accumulate over time and show significant effects later in life. "We therefore need cell culture systems that are able to model individual processes of human development," says Dr. Tanja Waldmann, group leader and scientist in the Department of in-vitro Toxicology and Biomedicine led by Professor Leist at the University of Konstanz.

Dr. Waldmann and her colleagues have developed an in vitro test system based on the differentiation of human embryonic stem cells into neuroectodermal progenitor cells. "These cells resemble the cells that are found during the early stages of neural tube closure," Dr. Waldmann explains. The researchers exposed stem cells to neurotoxic compounds during differentiation and studied the resulting effects.

Waldmann is specifically focussed on epigenetic cell alterations, i.e. changes of cellular properties that are not encoded in the underlying DNA sequences. Epigenetic mechanisms include DNA and histone modifications, including aberrant methylation and acetylation. Besides genetic changes, i.e. mutations, epigenetic modifications have been shown to lead to long-term effects and developmental disorders. "Epigenetic processes are highly dynamic, which is a potential reason why heritable genomic changes tend to accumulate over time," Waldmann explains. While some modifications are reversible, their accumulation leads to negative effects, including the aberrant regulation of genes. "Epigenetic modifications therefore have the potential to be used as a warning sign for the long-term effects of toxic substances on human development," Waldmann adds.

The use of epigenetics for the prediction of toxic effects



The toxicity tests generate huge amounts of data; these are analysed using the KNIME software, which was also developed at the University of Konstanz.

Some toxins have already been shown to have an effect on the entire range of epigenetic processes. One such toxin is arsenic, which has been shown to mediate changes in histone methylation and acetylation status as well as DNA methylation status. It has been proposed that arsenic has a direct biochemical effect on the activity of enzymes that catalyse the transfer of methyl groups. "Research into the effect of toxic chemicals on epigenetic processes is still in its infancy, and clear patterns and explanations are still lacking," Waldmann comments. To make matters worse, the impact of epigenetic modifications caused by pollutants can be very diverse. Basically, they lead to altered gene expression, which can over time lead to certain diseases, depending on which genes are affected.

Therefore, Dr. Waldmann and her doctoral student Nina Balmer are not only focussing on histone modifications, but also on changes in gene expression pattern. The test systems developed have already been used for studying the impact of various chemicals on human neurodevelopment. One such compound is valproic acid (VPA), which is a drug to treat epilepsy. VPA has been shown to target the process of neural tube closure, which is why children that were exposed to VPA in utero during this critical period showed symptoms of autism, lower IQ scores and symptoms of schizophrenia. It may also result in spina bifida or the death of the child. "Since our in vitro test system also models this particular development step, we included VPA in our studies," says Waldmann explaining which compounds were used for the studies and why. Waldmann's test system confirmed the negative effect of VPA on the development of the human nervous system. The researchers exposed the differentiating stem cells to VPA concentrations that were similar to the dose administered to people being treated for epilepsy. Exposure to VPA led to changes in histone modification status, gene expression pattern and also impaired the differentiation of the stem cells into ectodermal progenitor cells. "The results confirm the validity of the in vitro test system," Dr. Waldmann says.

Safety through versatility

The scientists are using the findings from the cell culture tests to draw conclusions on the situation in humans in order to assess the hazardous potential of a given chemical. The scientists' work is aimed at establishing a test battery consisting of many individual tests that target certain aspects in human development. The combination of the tests will then provide information on the impact of toxins on development as a whole. "Such a test battery would also be far superior to animal experiments as it would not only provide information on the effects of a chemical on overall development, but also allow the mechanistic investigation of toxic substances," says Waldmann, highlighting the advantages of the system. She sees animals as a kind of 'black box', as animal experiments provide information on the effects of a chemical, but not on the damage-related mechanisms.

Despite the positive findings, Dr. Waldmann nevertheless cautions against high expectations for the broad application of the test system in industry in the near future. "Epigenetic investigations are highly complex and therefore unsuitable for automated screening processes and high-throughput methods, at least for the time being," Waldmann concludes. She believes that gene expression profiling involving gene chips and functional endpoints such as the growth of nerve processes are much better suited for industrial applications as they have already been adapted to automated processes. "However, epigenetic investigations are very valuable as they can contribute to clarifying mechanisms of action and allow the diagnosis of small modifications before they manifest themselves in the phenotype," concludes Dr. Waldmann.

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Article

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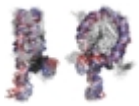

Epigenetics – heritable traits without changing the DNA sequence

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