BrainSpheres: testing neurotoxicity in human cells

Dr. David Pamies, University of Lausanne, Lausanne

The lessons learned in cancer research – where drug development has shown an extremely high failure rate (more than 90%)[1,2] – and in human disease studies, have shown us that the current models used are not optimal to predict human toxicity.[3-5] The cost per drug is estimated at $1.2–1.3 billion dollars,[6] and it takes approximately eight years to complete the whole process.[7] In addition, with the implementation of REACH and the need to test the large number of substances produced and used in the European Union, scientists and regulators agreed on the fact that the current test guidelines are too expensive and time consuming to allow the evaluation and classification of all compounds. Especially in the area of developmental neurotoxicity (DNT), where more and more evidence indicates that environmental chemicals contribute to subclinical neurodevelopmental toxicity,[8] the current OECD DNT guidelines for testing are so expensive and time consuming that they are not being performed routinely.[9,10] This results in a lack of information on DNT for most of the chemicals present on the market,[11,12] including high volume production chemicals, and it is becoming a very important public health concern.

A comprehensive *in vitro* DNT strategy has been suggested, consisting of a test battery that recapitulates key events taking place during brain development, such as migration, proliferation, differentiation, synaptogenesis, myelination, apoptosis, and neuronal network formation.[11] The previously described 3D human iPSC-derived brain model (BrainSpheres) recapitulates some of the key events of neurodevelopment.[13] BrainSpheres are very reproducible in terms of size and cellular composition, with no necrotic centers. They not only contain neurons and astrocytes but also functional oligodendrocytes with an axonal myelination between 40 and 50%, which is rarely observed *in vitro.*[13] Thus, we believe that BrainSpheres is a very complete system that could help to develop new DNT testing strategies. In recent years, we have used the BrainSpheres model to study the effects of neurotoxicants on different brain development processes. We assessed the developmental toxicity of pesticides[14] and the neurotoxicity of nanomaterials.[15] We also further developed several assays for DNT evaluation[16] and for the estimation of drug efficacy on glioblastoma tumors.[17] Here, we summarize the main advances of this model and its applications.

References:

1 Waring, M. J. *et al.* An analysis of the attrition of drug candidates from four major pharmaceutical companies. *Nat Rev Drug Discov* **14**, 475-486, doi:10.1038/nrd4609 (2015).
2 Lenz, H. J. & Stintzing, S. So much effort, so little progress? *J Natl Cancer Inst* **106**, doi:10.1093/jnci/dju282 (2014).
3 Akhtar, A. The Flaws and Human Harms of Animal Experimentation. *Camb Q Healthc Ethic* **24**, 407-419, doi:10.1017/S0963180115000079 (2015).
4 van der Worp, H. B. *et al.* Can Animal Models of Disease Reliably Inform Human Studies? *Plos Med* **7**, doi:ARTN e100024510.1371/journal.pmed.1000245 (2010).
5 Hartung, T. Look Back in Anger - What Clinical Studies Tell Us About Preclinical Work. *Altex-Altern Anim Ex* **30**, 275-291, doi:DOI 10.14573/altex.2013.3.275 (2013).
6 DiMasi, J. A., Grabowski, H. G. & Hansen, R. W. Innovation in the pharmaceutical industry: New estimates of R&D costs. *J Health Econ* **47**, 20-33, doi:10.1016/j.jhealeco.2016.01.012 (2016).
7 DiMasi, J. A., Feldman, L., Seckler, A. & Wilson, A. Trends in Risks Associated With New Drug Development: Success Rates for Investigational Drugs. *Clin Pharmacol Ther* **87**, 272-277, doi:10.1038/clpt.2009.295 (2010).
8 Grandjean, P. & Landrigan, P. J. Neurobehavioural effects of developmental toxicity. *Lancet Neurol* **13**, 330-338, doi:10.1016/S1474-4422(13)70278-3 (2014).
9 Kadereit, S., Zimmer, B., van Thriel, C., Hengstler, J. G. & Leist, M. Compound selection for in vitro modeling of developmental neurotoxicity. *Front Biosci-Landmrk* **17**, 2442-2460, doi:10.2741/4064 (2012).

10 Makris, S. L. *et al.* A Retrospective Performance Assessment of the Developmental Neurotoxicity Study in Support of OECD Test Guideline 426. *Environ Health Persp* **117**, 17-25, doi:10.1289/ehp.11447 (2009).
11 Bal-Price, A. *et al.* International STakeholder NETwork (ISTNET): creating a developmental neurotoxicity (DNT) testing road map for regulatory purposes. *Arch Toxicol* **89**, 269-287, doi:10.1007/s00204-015-1464-2 (2015).
12 Crofton, K. M., Mundy, W. R. & Shafer, T. J. Developmental neurotoxicity testing: A path forward. *Congenit Anom* **52**, 140-146, doi:10.1111/j.1741-4520.2012.00377.x (2012).
13 Pamies, D. *et al.* A Human Brain Microphysiological System Derived from Induced Pluripotent Stem Cells to Study Neurological Diseases and Toxicity. *Altex-Altern Anim Ex* **34**, 362-376, doi:10.14573/altex.1609122 (2017).
14 Pamies, D. *et al.* Rotenone exerts developmental neurotoxicity in a human brain spheroid model. *Toxicol Appl Pharmacol* **354**, 101-114, doi:10.1016/j.taap.2018.02.003 (2018).
15 Leist, M. *et al.* Consensus Report on the Future of Animal-Free Systemic Toxicity Testing. *Altex-Altern Anim Ex* **31**, 341-356, doi:DOI 10.14573/altex.1406091 (2014).
16 Zhong, X. *et al.* Antidepressant Paroxetine Exerts Developmental Neurotoxicity in an iPSC-Derived 3D Human Brain Model. *Front Cell Neurosci* **14**, 25, doi:10.3389/fncel.2020.00025 (2020).
17 Plummer, S. *et al.* A Human iPSC-derived 3D platform using primary brain cancer cells to study drug development and personalized medicine. *Sci Rep-Uk* **9**, doi:ARTN 140710.1038/s41598-018-38130-0 (2019).