Research Interests – Professor Dr. Marcel Leist

Die Arbeitsgruppe befasst sich mit **In-vitro-Toxikologie** und **biomedizinischen Fragen** im **Bereich des Nervensystems.** Bei vielen der neu entwickelten Verfahren handelt es sich um **Alternativmethoden zum Tierversuchsersatz.** Die Testmethoden werden

(1) weiterentwickelt, um einen höheren Probendurchsatz zu erlauben (Screens);

(2) weiterentwickelt, um neue Endpunkte zu erfassen oder um Leistungsparameter zu verbessern;

(3) von ihrer mechanistischen Basis her weiter erforscht;

(4) um zusätzliche zelluläre Elemente erweitert (Organoide);

(5) auf ihren Anwendbarkeitsstatus (Robustheit, Relevanz, Vorhersagekraft) hin evaluiert;

(6) um mathematische Modelle und Konzepte erweitert.

Few examples are given:

Neurodegeneration by proteasome inhibitors

It has often been claimed that disturbances of the ubiquitin proteasome system (UPS) are linked to neurodegeneration. Direct evidence comes from treatments of people and animals with proteasome inhibitors. Systemic treatment with proteasome inhibitors triggers Parkinsonian pathology in rodents, and exposure of chemotherapy patients to the proteasome inhibitor bortezomib is associated with a very high frequency of peripheral nerve damage. It is our long-term interest to clarify mechanisms of the associated neuronal death, and find potential interventions.

Recycling of cell surface carbohydrates

We have developed a method to visualise surface sialic acids on neurons. The aim of this project is to optimise experimental conditions that allow a selective visualisation of sialylated lipids and proteins, and to follow their fate on complex cells like neurons (recycling, axonal transport, re-distribution upon differentiation). As follow-up, we will study surface sialylation during human neurodevelopment.

Pesticide toxicity predictions

Our current assays for molecular and morphological changes of cells have a very high readiness status and are applied to predict pesticide toxicity. They do, however, not sufficiently capture the functional capacity of neurons and of the network they form. Therefore, a long-

term goal is to establish an assay of electrical network activity based on microelectrode arrays (MEAs), on which cells can be cultured. We are especially interested in newer classes of pesticides and in their comparison to the group of neonicotinoids and the two major classes of pyrethroids.

Mitochondrial toxicity and stress resilience

Our main hypothesis is: The toxicity is not only determined by the direct potency and efficacy of a mitochondrial inhibitor at a given target, but also by the exact mode of target interaction, by the metabolic state and reserve capacity of a given cell type, and by adaptive functions (resilience) triggered within some, but not all cells. We want to clarify key metabolic and signalling factors determining the threshold for mitochondrial toxicity, using and comparing a broad panel of respiratory chain inhibitors, and triggering, as well as measuring defined metabolic situations of cells. We study on the biochemical level the degree of inhibition of various complexes. We characterised > 20 mitochondrial inhibitors and identified a pharmacophore for such effects and we will test unknown chemicals that have been found in a virtual screen for the pharmacophore for mitochondrial inhibition and toxicity.

Development of advanced test methods and necessary technology

A main topic of the Chair is to develop new methods to be used in human health assessment. Our neurodevelopmental toxicity test (termed UKN1), developed eight years ago, is used in several international projects to explore toxicity.

Another of our assays (UKN5 – PeriTox assay) has been used very successfully to identify peripheral neurotoxicants. We follow various strategies to incorporate new endpoints into the assay (e. g. activation of pain receptors). To allow long-term neuronal cultures, we combine them with supporting cells like Schwann cells or astrocytes.

We also established 3D cultures (neuronal organoids) that can be cultured for months and incorporate many different cell types. Together with chemists, we develop new matrices for such cultures.

Good scientific practices

Various activities towards research and establishment of good scientific practices are being pursued. One is to develop procedures for the incorporation of biokinetics data into in vitro data interpretation. Biokinetics data refer to the distribution phenomena of a drug in a cell culture dish, and they are derived both from direct measurements and biophysical calculations. In the past, we characterised e. g. binding of drug to plastic surfaces, and we will continue to study binding to lipids and proteins as medium constituents. This is part of a large activity, within the international good cell culture practice (GCCP) consortium. We have just updated the 2005 GCCP document towards a GCCP 2.0 version. One important activity in

this direction is the extension of GCCP for microphysiological systems (MPS), i. e. 3D complex cultures and organoids, and we will bring world-wide stakeholders together to establish a consensus document.

Characterisation of new drug candidates

Due to the availability of multiple test methods in the lab, we interact with several groups in chemistry concerning the profiling of compounds. We designed iron chelators that are transported into the brain. The biological activity of several such synthetic chelators (synthesised at the University of Nottingham) has been tested, and they are promising agents to be used as experimental Parkinson's disease therapeutics. In parallel we continue collaboration with our Brazilian guest researcher Elaine Fagundes on compounds derived from the Brazilian fauna. A special focus is on antioxidant properties and on a peptidic compound from spider venom as drug candidates.

Development of improved read across methods for toxicity prediction

Read across (RAX) is a toxicological procedure that uses chemical structural features relationships to infer toxicological properties of unknown compounds from those of known compounds. We have in the past time used valproic acid (VPA) analogs to study ways of improving read-across. These include improved structure-activity relationship (QSAR) algorithms, incorporation of biochemical data, and incorporation of biological response data.