Liver, heart, kidney and brain drug-induced toxicities currently account for more than 70% of drug attrition and drug withdrawal. Porsolt together with Fluofarma has developed a range of organ-specific cell-based assays to better predict the toxicity potential of drug candidates.

We offer phenotypic functional toxicity assays and investigate the signaling pathways involved in the toxicity induced by the drug compound, using highly predictive cellular models.
**Molecular mechanisms of hepatotoxicity**

The use of multiple readouts in microplate format allows for the exploration of a panel of toxicity mechanisms, providing the best sensitivity for profiling the potential toxic risks from test compounds.

- **Case study: hepatotoxicity profiling of compound XXX**

Hepatotoxicity has been detected in rat hepatocytes, with the exception of steatosis that can only be detected in human hepatocytes.
**Nephrotoxicity**

Human Renal Proximal Tubule Epithelial Cells (HRPTEpC) are a valuable tool to study nephrotoxicity, as particularly vulnerable to toxic effects of drugs, because their physiological role exposes them to high levels of circulating toxins.

Cytolysis, as the ultimate consequence of gross cytotoxicity, or specific readouts, such as lysosomal activity or Mitochondrial Membrane Potential, related to the mechanism of action, can be measured to evaluate potential toxicity of test articles.

![Graph showing Lysosomal activity and Mitochondrial Membrane Potential](image)

**Cardiotoxicity**

Human induced pluripotent stem cell derived cardiomyocytes (hiPSC-CMs) are increasingly used to evaluate cardiotoxicity in the early stages of the drug discovery process, as they express all the relevant cardiac ion channels (K+, Ca2+, Na+) and allow for integrated measures (not restricted to a single ion channel). Any irregularity in their spontaneous beating can provide a sign of potential toxicity.

![Graph showing iCell® cardiomyocytes and Moxifloxacin](image)

**Calcium assay**
Calcium is the link between excitation and contraction of the cardiomyocytes. Analysis of Calcium transients (rate and peak pattern) therefore provides an obvious and simple output.

**MEA assay**
MEA technology allows for the recording of extracellular field potential waveforms, which are analogous to clinical electrocardiogram recordings.

Ionic current measurements in ion channel cell lines are also available (e.g. hERG).
**Neurotoxicity**

Fluofarma offers rodent (rat and mouse) primary neuronal cultures and human induced Pluripotent Stem Cells (hiPSCs) derived neurons to evaluate neurotoxicity. The most commonly used phenotypic readout to measure the neuronal response to neurotoxins is cell death. Neurite outgrowth is also a parameter of choice, as a sensitive descriptor directly reflecting the health state of neurons.

Cytolysis, rat primary cortical neurons

Neurite outgrowth iCell® DOPA neurons

Specific readouts, dependent on the mechanism of action, such as caspase 3/7 activation or Mitochondrial Membrane Potential, can also be analyzed.

**Genotoxicity**

As drug-induced genotoxicity often triggers DNA Double Strand Breaks (DSB), which may ultimately lead to oncogenic mutations, Fluofarma can evaluate this specific DNA damage through the quantification of γ-H2AX induction level (one of the earliest events after DNA DSB occurrence, as an anchor point for DNA repair proteins).

γ-H2AX induction level in cancer cell lines

HeLa cells stained for γ-H2AX (green) and DAPI (blue)