In vitro Pharmacology: Cellular Pharmacokinetics

Entry of compounds into cells is a crucial property for drugs that act on intracellular targets and is the most common reason for a drop in efficacy between biochemical and cellular screening assays. Therefore, measurement of intracellular drug concentration can be of great help in determining the structural features limiting drug entry into cells.

In addition to entering cells, some compounds, mainly those positively charged at physiological pH, have the ability to accumulate inside the cell, and reach intracellular concentrations that are up to several hundred times higher than extracellular. Most of the compound is then present in acidic compartments of the cell, but is gradually released as the extracellular concentration of the drug decreases. Some compounds, although highly accumulated in cells, are rapidly released, whereas others are retained in cells for longer periods of time. These features have the profound effect on overall drug pharmacokinetics and modulation of these properties can help design molecules that are more likely to fit a desired product profile in terms of administration frequency and safety.

In cellular pharmacokinetics Fidelta offers:

- Expertise in measurement of drug accumulation and retention in target cells of various origins (e.g. primary cultures of human cells: polymorphonuclear leukocytes, lymphocytes, erythrocytes, bronchial epithelium, lung fibroblasts, as well as various cell lines) (Figure 1)
- Reliable LC-MS/MS quantification of compounds
- Finding a suitable cell line model for cellular pharmacokinetics
- Development of *in silico* prediction models for cellular pharmacokinetics (Figure 2)
- Finding *in vivo* PK parameters affected by specific cellular pharmacokinetics properties
- Development of fluorescent analogues of drugs with similar PK/PD properties (Figure 3)

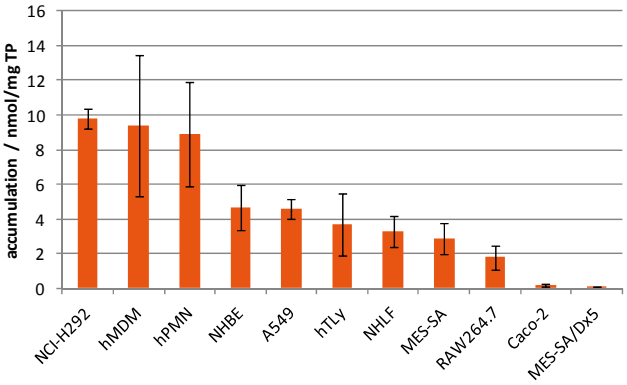

Figure 1. Accumulation of azithromycin in human primary cells: monocyte derived macrophages (hMDM), polymorphonuclear leukocytes (hPMN), bronchial cells (NHBE), T-lymphocytes (hTLy), lung fibroblasts (NHLF), and cell lines of various origin: lung carcinoma (NCI-H292, A549), uterine sarcoma (MES-SA and MES-SA/Dx5 with overexpressed P-glycoprotein (ABCB1, MDR1)), colorectal adenocarcinoma (Caco-2) and murine monocytic-macrophage cell line (RAW254.7). Results represent mean values of 3-8 experiments. (Stepanić et al. 2011, Munić et al. 2010)

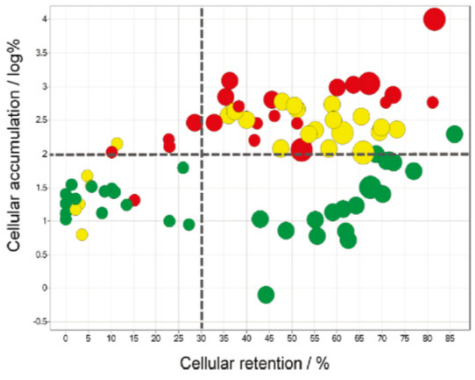

Figure 2. Modelling cellular accumulation and retention of macrolide compounds in the NCI-H292 cell line based on lipophilicity parameter ChromlogD (color) and number of positive charges in molecule (size) (Stepanić et al. 2011)

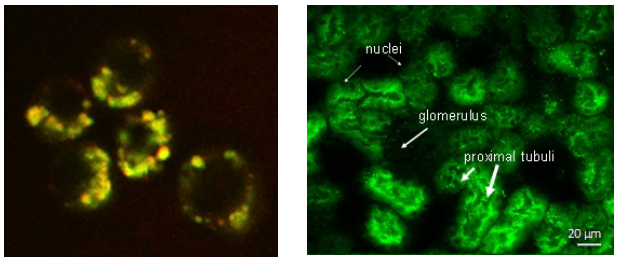

Figure 3. Distribution of fluorescent azithromycin analogue (green) within J774A.1 cells (overlap with lysosomal marker LysoTracker Red) and in murine kidney after intraperitoneal administration (Matijašić et al. 2012).

References
Stepanić et al. 2011, J Med Chem 54, 719; Munić et al. 2010, Eur J Pharm Sci 41, 86; Matijašić et al. 2012, Pharmacol Res 66, 332

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