Novel Cell-based Test Systems for Drug Screening

Christoph Wiesner, Anna Stierschneider, Victoria Sarne, Doris Ripper, Dominik Schild, Dana Mezricky, Christian T. Klein, Harald Hundsberger

[a]*Department of Medical and Pharmaceutical Biotechnology, IMC University of Applied Sciences Krems, Krems an der Donau 3500, Austria.*

E-mail: christoph.wiesner@fh-krems.ac.at

With approximately 8.8 million deaths in 2015 cancer represents the second leading cause of mortality worldwide[1]. One defining feature of cancer is the development of tumors from single cells that begin to proliferate abnormally and to grow beyond their usual boundaries, invade adjoining parts of the body and spread to other organs (metastasis)[2]. Disruption of tightly regulated processes such as cell cycle, cell adhesion, cell differentiation, migration and cell death are predominant in cancer development.
Although the pharmaceutical industry spent millions of Euros on the research for new, more effective drugs, the attrition rates in clinical development are still very high. This clinical failure can be, at least partially, attributed to a lack of clinical efficacy, indicating a strong need for highly predictive test systems for the screening of new therapeutic drugs[3].

Our research at the IMC Krems focuses on the establishment of innovative test systems for the rapid identification and optimization of novel synthetic or biological drug candidates and the discovery of drug targets and biomarkers. We are developing high-content *in vitro* disease models for hit identification and hit to lead optimization. At present, our portfolio consists of cell- and tissue based models for cancer, immune disorders, leaky gut syndrome and skin diseases[4-7].
For cancer screening, two-dimensional cell culture models (2D) on plastic, filter inserts or gold film electrodes (impedance measurement) are established to provide basic information on cytotoxicity, cell proliferation, (de)differentiation, cell migration and penetration in high throughput assays. For a better physiological screening, three-dimensional (3D) tissue models, including homo- and heterotypic spheroids, that mimic *in vivo* conditions and the functions of living tissue more accurately, are developed. The novel test system has been successfully established to study tumor cell proliferation, invasion, response to toxicants (induction of cellular apoptosis), and can be used for various other applications[8-11]. These methods are compatible with automated high-throughput screening or bio-imaging and high-content phenotype-based drug discovery. To facilitate the identification of promising druggable targets, we are currently establishing a large panel of pathway-specific reporter cell lines allowing the evaluation of specific signaling pathways in tumor spheroids.
In summary, these sensitive and reproducible test systems permit an imaged based screening of morphological changes (e.g. cellular differentiation, migration, gene expression), predict *in vitro* toxicity, and suggest pathways or molecular targets (pathway profiling) of novel compounds and are therefore a useful tool to elucidate the mode of action of new lead compounds.

References:

[1]. Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C et al. (2012). *IARC CancerBase* No. 11

[2]. A. Eger, W. Mikulits (2005). *Drug Discov. Today* 2: 57–63

[3]. Riedl A, Schlederer M, Pudelko K, Stadler M, Walter S, Unterleuthner D, et al. (2017). *J Cell Sci.*:1;130(1):203-218.

[4]. Hundsberger H, Koppensteiner A, Hofmann E, Ripper D, Pflüger M, Stadlmann V, et al. (2017). *SLAS Discov*. 1:2472555217697435.

[5]. Pretsch A, Nagl M, Schwendinger K, Kreiseder B, Wiederstein M, Pretsch D et al. (2014). *PLoS One*. ;9(6): e97929.

[6]. Pflüger M, Kapuscik A, Lucas R, Koppensteiner A, Katzlinger M, Jokela J et al. (2013). *J Biomol Screen*. 2013 Jan;18(1):67-74.

[7]. Wiesner C, Pflüger M, Kopecky J, Stys D, Entler B, Lucas R. et al. (2008). *GMS Krankenhhyg Interdiszip*. 11;3 (1).

[8]. Kreiseder B, Holper-Schichl YM, Muellauer B, Jacobi N, Pretsch A, Schmid JA, et al. (2015) *PLoS One*. 20;10(3):e0119402.

[9]. Genov M, Kreiseder B, Nagl M, Drucker E, Wiederstein M, Muellauer B, et al. (2016). *J Cancer*. 12;7(5):555-68.

[10]. Kreiseder B, Orel L, Bujnow C, Buschek S, Pflueger M, Schuett W, et al. (2013). *Int J Cancer* 1;132(3):521-30.

[11]. Amatschek S, Lucas R, Eger A, Pflueger M, Hundsberger H, Knoll C, et al. (2011). *Br J Cancer.* 1;104(3):469-79.