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Searching for the needle in the haystack – targeted identification of pharmacologically active natural products

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Natural product-derived or -inspired drug discovery continues to be relevant for the development of innovative medicines. However, screening of extracts and identification of bioactive compounds remain major challenges in natural product-based drug discovery. In recent years a wide range of new technologies and tools have been established in the biosciences and in analytical chemistry that enable new approaches. These new possibilities can be summarized with a few keywords such as: miniaturization, on-line analysis of complex samples, chemometric data analysis, functional assays, high-content screening, study of molecular modes of action, and systems oriented approaches towards the characterization of drug effects *in vitro* and *in vivo*.

Over the past years we explored some of these methodologies in our lab and, as a consequence, established a technology platform for miniaturized natural products-based lead discovery. This platform includes 2D-barcoded liquid extract libraries in 96-well format, HPLC-based micro-fractionation for off-line bioactivity assessment, simultaneous on-line spectroscopy (PDA, HRMS, and MS/MS), and off-line microprobe NMR spectroscopy. The platform is generically applicable with mechanism-based and functional assays in the 96-well MTP format and serves as a core for collaborative projects in various therapeutic areas.

Use of the technology platform will be illustrated with selected examples, including the discovery of new allosteric $GABA_A$ receptor modulators and image-based high content screening for compounds targeting key signaling pathways in melanoma. The power of miniaturization will be discussed with the identification of a selectively anti-proliferative cucurbitane derivative from just few mg of a plant extract, and the value of activity profiling data for subsequent structural optimization will be highlighted with the example of the $GABA_A$ receptor modulating lead compound SCT-66. We are currently also using our HPLC profiling approach for the assessment of potential cardiac toxicity of herbal drugs. Dehydroevodiamine and hortiamine, two alkaloids from the traditional Chinese herbal drug *Evodia rutaecarpa*, were identified as potent I_{Kr} blockers with proarrhythmic effects *in vitro*, and *in vivo* in rodent and dog models.