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A system-wide approach for the identification of druggable proteins in a complex mixture

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Background

In contrast to target-based drug discovery, phenotypic screening discloses the effect of a compound on a biological system without revealing its mode of action or its interaction sites. Phenotypic screening has delivered several new valuable drugs, however, the major challenge remains target deconvolution (1). In recent years, “omics” techniques and bioinformatics have brought significant advances to target identification in drug discovery phenotypic screening. However, such analyses can become highly complex, costly and time-intensive (2). More straightforward methods that are based on affinity pull-down or DNA tags bound to the compound are applicable to chemically synthesized compounds only. Thus, natural compounds having the highest hit rate are excluded from such analyses (2).

Technology

Scientists from the Max-Planck Institute of Molecular Plant Physiology have developed an easy and efficient way to screen complex compound libraries of any origin for the presence of compounds which form stable complex with the macromolecular target. This approach can be multiplexed thus allowing screen for several targets in one experiment. This alternate approach relies on a global analysis of protein-bound small molecules using metabolomics techniques. The principle of this approach is based on the supposition that small molecules/metabolites interacting with proteins are forming a stable complex and will fractionate together (3). Thus, by applying size separation of proteins and their ligands by co-fractionation and subsequent size exclusion chromatography or size filtration, unbound and non-covalently-bound ligands will be found in different eluates following size separation. Subsequently, the different samples are analyzed by LC/MS (Liquid-chromatography mass spectrometry).

This approach allows on the one hand the identification of **new endogenous compounds** present in human systems that bind to macromolecules, such as proteins, RNA, DNA, or membranes. On the other hand it enables the **identification of natural or chemically synthesized small molecules bound to their target as well as multiplexing of several targets.** This technology will dramatically reduce time needed for screening and thus will result in a **significant cost advantage**.

Patent Information:

European priority application has been filed in May 2016.

Literature:

(1) Moffat, J.G. et al., *Nat Rev Drug Discov* 16, 531–543 (2017)
(2) Lee, H. & Lee, J.W. *Arch. Pharm. Res.* 39:1193–1201 (2016)
(3) Veyel, D. et al., *Sci Rep* **7**, Article number: 42387 (2017)