Institut Européen de Chimie et Biologie

I E C B

Unbiased approaches in the discovery of biologically active small molecules and druggable targets.

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The pharmaceutical industry typically looks for treatments based on the hypothesis that a target may be responsible for a disease. In contrast, human genetics tend to identify cellular processes subject to imbalances that need to be corrected. The complexity of biology does not allow for the use of purely hypothesis-based strategies but rather prompts towards the establishment of discovery-driven approaches. Natural products and synthetic small molecules are central players in chemical biology studies. They promote the perturbation of processes underlying diseases and facilitate the discovery of biological targets that can be validated for therapeutic intervention. For example, small molecules have been shown to accurately tune a single function of pluripotent proteins in a reversible and dose- dependant manner with temporal resolution that is hardly achievable by current molecular biology methods. The high potential of unbiased approaches will be illustrated by 1. the identification of the oncogene *SRC* as a target for G-quadruplex targeting small molecules based on genome-wide sequencing and 2. the discovery of a lysine acetyl transferase as a regulator of nuclear shape and cellular fitness of Hutchinson-Gilford Progeria Syndrome affected cells from affinity pull-down, proteomics and small molecule labeling in cells.