

ReBiL: A Powerful Platform to Analyze Protein-Protein Interactions (PPIs) and Screen for Antagonists and Agonists of PPIs In Vivo

INVENTION: Drs. Leo Li and Geoffrey Wahl at the Salk Institute have developed a novel cell-based screening platform for the characterization of protein-protein interactions (PPIs), and the discovery of compounds that can modulate these interactions. This technology combines recombinase-mediated cassette exchange (RMCE), an inducible protein expression system and the bi-molecular luciferase complementation (BiLC) assay to create a broadly applicable method to study PPIs in real time in living cells or cell lysates. The platform, designated ReBiL (**R**ecombinase-**e**nanced **B**iLC), robustly detects transient and dynamic PPIs with high reproducibility, and enables identification of novel intracellular protein interaction partners. Our investigators have shown utility of ReBiL in the screening and characterization of PPI antagonists and agonists in high-throughput formats.

APPLICATIONS:

- Characterization of transient and dynamic PPIs
- Characterization of membrane-associated PPIs
- Identification of novel PPIs
- High throughput screening (HTS) of compound libraries for modulation of PPIs.
- Characterization of PPI antagonists and agonists

ADVANTAGES:

- Portable and straightforward cloning and cell line preparations
- Highly sensitive and robust
- Can be used with whole cells or cell lysates
- Can interrogate low affinity PPIs, and has a broad range of sizes for target proteins
- Can access target specificity and cell permeability simultaneously
- Captures all classes of PPI antagonists: interface binders, conformation tappers, and allosteric inducers
- Statistically significant identification of hits in high-throughput screens
- Identify compound binding sites and mechanism of action

STAGE OF DEVELOPMENT:

- This technology has been validated using at least three (3) drug candidates, one (1) FDA approved cancer therapeutic, and applied to cytoplasmic and membrane bound proteins
- Our scientists have developed powerful tools for the investigation of multiple major oncogenic pathways including p53 and Myc.

BACKGROUND: The exploration of PPIs as a strategy for identifying new drug targets holds great potential, but is subject to various technical difficulties not associated with enzyme or receptor targets. Current methods for evaluating PPIs are not able to monitor low affinity interactions in vivo, and conventional biophysical assays for compounds that modify these interactions are unable to sufficiently assess bioavailability or functionality of PPI agonists and antagonists in living cells. The ReBiL screening platform overcomes many of the current limitations associated with drug discovery and PPIs, and has the potential to expand the field of drug discovery to include a whole new class of druggable targets.

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PATENT STATUS: U.S. patent application US2015-0010932A1 is pending



PUBLICATIONS:

- Li, *et al.* 2014. A versatile platform to analyze low-affinity and transient protein-protein interactions in living cells in real time. *Cell Rep.* 2014 December 11; 9(5): 1946–1958
- Li, *et al.* 2018. Facile real time detection of membrane colocalization of RAS superfamily GTPase proteins in living cells. <https://www.biorxiv.org/content/early/2018/07/15/369587>
- <http://www.salk.edu/news-release/salk-scientists-unveil-powerful-method-to-speed-cancer-drug-discovery/>

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