

## Introduction

G protein-coupled receptors (GPCRs) are targets of more than one-third of currently prescribed medications. Approximately one-third of the nonolfactory GPCRs in the human genome are orphan GPCRs whose natural ligands are unknown. Because many of these sparsely annotated GPCRs will probably represent fruitful future therapeutic targets, identifying drug-like chemical leads for the entire family of druggable GPCRs represents a major goal for chemical biology. Unfortunately, interrogating the druggable GPCRome in a parallel and simultaneous fashion is currently technologically and economically unfeasible. There many functional assay which has been developed for studying GPCR activity, however none of them are well suited for the parallel and simultaneous genome-wide interrogation of the druggable GPCRome. Measurement of G protein-independent Beta-Arrestin recruitment provides a feasible and universal assay platform because nearly all the tested GPCRs can induce arrestin translocation. Thus Presto-Tango facilitates the rapid, efficacious, parallel and simultaneous profiling of biologically active compounds across essentially the entire human druggable GPCRome.

## **PRESTO-TANGO as an open-source resource for interrogation of the druggable human GPCRome**

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## Abstract

G protein-coupled receptors (GPCRs) are essential mediators of cellular signaling and are important targets of drug action. Of the approximately 350 nonolfactory human GPCRs, more than 100 are still considered to be ‘orphans’ because their endogenous ligands remain unknown. Here, we describe a unique open-source resource that allows interrogation of the druggable human GPCRome via a G protein-independent b-arrestin-recruitment assay. We validate this unique platform at more than 120 nonorphan human GPCR targets, demonstrate its utility for discovering new ligands for orphan human GPCRs and describe a method (parallel receptorome expression and screening via transcriptional output, with transcriptional activation following arrestin translocation (PRESTO-Tango)) for the simultaneous and parallel interrogation of the entire human nonolfactory GPCRome.