How CRISPR Transforms Modern Drug Discovery

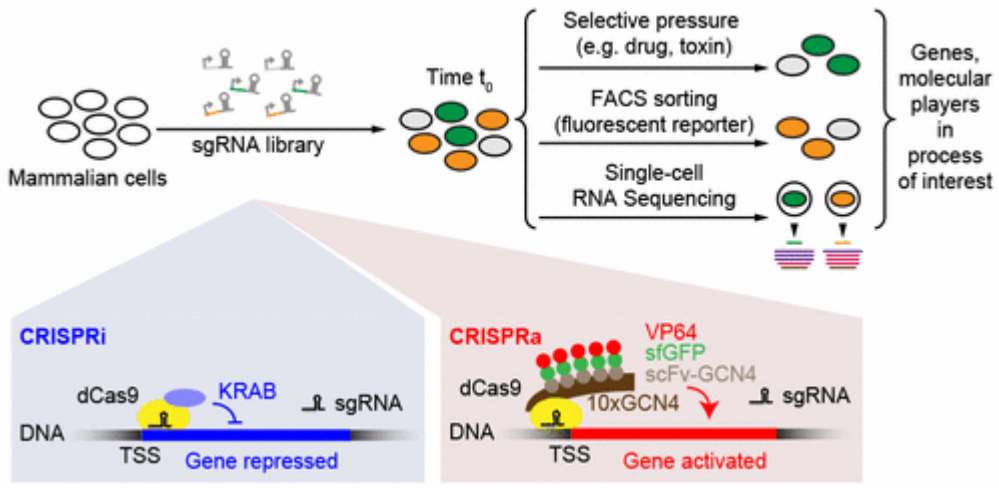
Nov. 13, 2017 by Alfred Ajami

Consensus seems universal and the news about it flows literally by the minute over gene editing as a future therapy, complete with patent sagas and ethical conundrums. But at the bench, CRISPR's impact is also proving disruptive, and revolutionary, soon to irrevocably change the mechanics of drug discovery and pre-clinical development in multiple ways. One particular set of CRISPR applications should be on every drug hunter's radar: disease relevant cellular reporter models manipulated to reflect disease phenotypes.

While the transition away from in vitro and immortalized cell assay systems has been underway over the last decade, the pace increased with the advent of easily manipulated stem cells to create fit-for-purpose biochemical and high content, high throughput screens. The principal accelerator here has been CRISPR editing to provide organotypic and disease specific models, including direct application of patient-sourced cells and assembled organoids (disease and control) as platforms for drug SAR and efficacy testing.

As Andrew Bassett from the Wellcome puts the matter: "such cells can be generated in sufficient numbers to be able to perform whole genome genetic screens to identify molecular and cellular mechanisms of disease and therapeutic targets, and also for high throughput drug screening to identify compounds that may be able to revert the disease phenotype. Differences between patient-derived and control cells can be used to identify potential therapeutic targets or agents." (Ref. 1). A compelling example in an underserved area of research lies in the development of CRISPR driven new assays for glioblastoma (Ref. 2).

Diving deeper reveals how powerful CRISPR manipulation can be in effectively affording knock-in, through activation (CRISPRa), or knock-out, through interference (CRISPRi), of traits/phenotypes subject to targeting and modulation by candidate drugs (Refs. 3-5 and graphic below taken from Ref. 4). The technology is also extensible to organoids, deriving further informational value from this more physiologically meaningful cell platform (Refs. 6,7).



Practical applications of CRISPR in cell reporter assays are also noteworthy for by-passing the inconsistencies (or effective impossibility) of either durable or transient transfection in attaching the reporter to a target regulatory element at specific loci of a gene. Representative implementations, with benchmark methodology, include tagging with luciferases and luminescent proteins for both high throughput and high content, imaging assays (Refs. 8-10).

Is CRISPR panacea for discovery and validation assays? The answer depends on the cell-based context, so the exercise left to the reader is to examine the full spectrum of modalities (Ref. 11) where the influence of CRISPR methodology is more likely to be felt.

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