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Title: **Colorful Chemical Genetics**

Abstract

With the successful result of Human Genome Project, we are facing the problem of handling numerous target genes whose functions remain to be studied. In chemical genetics, instead of using gene knock-out or overexpression as in conventional genetics, a small molecule library is used to disclose a novel phenotype, eventually for the study of gene function. While a successful chemical genetics work will identify a novel gene product (target protein) and its on /off switch, the small molecule complement, and thus chemical genetics promises an efficient “two birds with one stone” approach, the most serious bottleneck of modern chemical genetics is the step of target identification. The currently popular affinity matrix technique is challenging because the transformation of the lead compound into an efficient affinity molecule without losing the biological activity is not easy, requiring intensive SAR studies. To surrogate the well known problem, our group has developed a linker tagged library and has successfully identified multiple target proteins so far. While successful, the affinity matrix technique requires a breakdown of the biological system to pool the proteins into one extract, which inherently introduce a lot of artifacts, such as dilution and abolishing the biological environment, etc.

As the next generation of tagged library, we are currently developing fluorescence tagged libraries for in situ target identification and a visualization of the biological events using Diversity Oriented Fluorescence Library Approach (DOFLA). The basic hypothesis is DOFLA of the same fluorescence scaffold, but with various diversity elements *directly attached around the core*, may selectively respond to a broader range of target proteins in intact biological system and facilitate the mechanism elucidation and target identification. The high throughput strategy using colorful chemical genetics will open the efficient road to chemical genomics and in vivo bioimaging probe development.