Encoded display of chemical libraries as a versatile selection tool for discovering protein ligands

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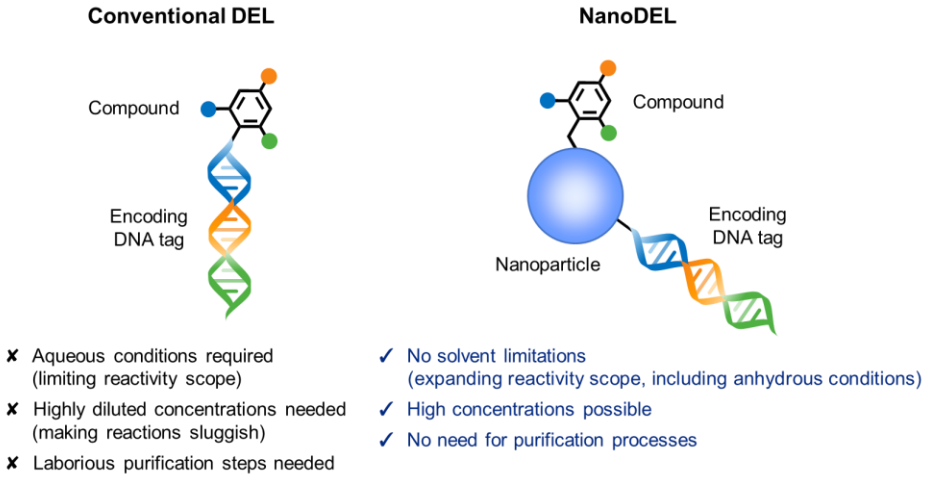
DNA-encoded libraries (DELs) have emerged as a powerful tool for rapid discovering potent protein ligands. However, current DEL technology has inherent limitations stemming from the insolubility of DNA in organic solvents, which restricts the reactivity scope and structural diversity of synthesized compounds. Here, we have developed a strategy called nanoDEL, where library molecules and DNA tags are displayed on the surface of nanoparticles. Since nanoparticles are well-dispersed in both organic solvents and aqueous solutions, the synthesis of DELs can be accomplished using well-established organic solvent-based reaction conditions, thereby obviating the need to develop DNA-compatible, aqueous reaction conditions. In addition, unlike conventional DEL methods, nanoDEL technology streamlines the library synthesis by eliminating the need for laborious purification steps. The potential of the nanoDEL technology was validated by the affinity-based selection against streptavidin as a model system and successfully applied to the discovery of potent small-molecule inhibitors for a kinase and peptidomimetic inhibitors targeting a protein-protein interaction, exhibiting dissociation constants in the nanomolar range. Collectively, we believe that our nano-DEL technology will be highly useful in facilitating chemical biology research and discovering drug candidates.



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