On-Nanoparticle Display of Encoded Chemical Libraries as a Powerful Tool for Discovering Potent Protein Ligands

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DNA-encoded library (DEL) technology has emerged as a powerful selection tool for discovering bioactive molecules. DELs enable the screening of chemical libraries containing up to billions of molecules, leading to the rapid discovery of potent protein ligands. However, conventional DEL method has inherent limitations stemming from the poor solubility of DNA in organic solvents. Due to the insolubility of DNA in most organic solvents, all reactions used for DEL synthesis require aqueous conditions. This significantly restricts the reactivity scope and structural diversity of synthesized compounds. Moreover, since DNA solubility remains insufficient even in water, reactions must be carried out in highly diluted concentrations (typically less than 1 mM), making reactions sluggish.

In this study, we have developed an innovative strategy called nanoDEL, where library molecules and coding DNA tags are displayed on the surface of nanoparticles. Notably, nanoparticles are well-dispersed in both aqueous solutions and organic solvents. This characteristic allows the nanoDEL method to utilize well-established reaction conditions without the need to develop DNA-compatible reaction conditions for libray synthesis. In addition, unlike conventional DEL synthesis which require laborious purification processes (*e.g.*, HPLC and lyophilization) in each step, nanoDEL technology eliminates the need for purification steps throughout library synthesis by utilizing nanoparticles as solid supports. The potential of the nanoDEL technology in discovering potent ligands against biological targets was successfully validated through affinity-based selections. On-nanoparticle selections yielded highly effective small-molecule inhibitors for a kinase and peptidomimetic inhibitors targeting protein-protein interaction, exhibiting remarkable activities in the nanomolar range.

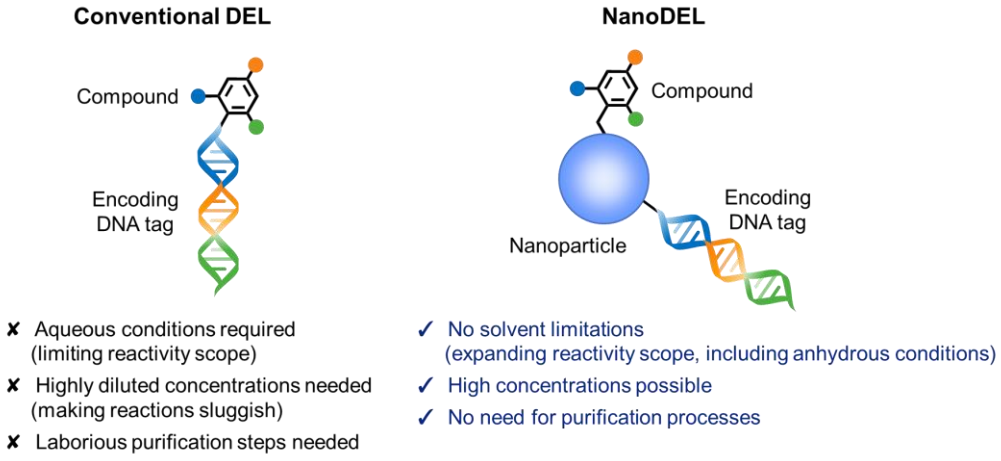

Figure 1. Comparison of conventional DELs and nanoDEL system.