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Research Interests:

DNA-encoded library, Targeted protein degradation, Peptidomimetics

Selected Publications:

1. Lee, S.; Kwon, H.; Jee, E. K.; Kim, J.; Lee, K. J.; Kim, J.; Ko, N.; Lee, E.; **Lim, H. S.** "Synthesis and structural characterization of macrocyclic a-Abpeptoids and their DNA-encoded library." *Org. Lett*. **2024**, *26*, 1100.
2. Lee, Y.; Heo, J.; Jeong, H.; Hong, K. T.; Kwon, D. H.; Shin, M. H.; Oh, M.; Sable, G. A.; Ahn, G.; Lee, J.; Song, H. K.; **Lim, H. S.** "Targeted degradation of transcription co-activator SRC-1 via the N-degron pathway." *Angew. Chem. Int. Ed.* **2020**, *59*, 17548.
3. Lee, Y.; Yoon, H.; Hwang, S. M.; Shin, M. K.; Lee, J. H.; Oh, M.; Im, S. H.; Song, J.; **Lim, H. S**. "Targeted inhibition of the NCOA1/STAT6 protein-protein interaction." *J. Am. Chem. Soc.* **2017***, 139*, 16056.
4. Oh, M.; Lee, J. H.; Moon, H.; Hyun, Y. J.; **Lim, H. S.** "A chemical inhibitor of the Skp2/p300 interaction that promotes p53-mediated apoptosis." *Angew. Chem. Int. Ed.* **2016**. *55*, 602.
5. Oh, M.; Lee, J. H.; Wang, W.; Lee, H. S.; Burlak, C.; Im, W.; Hoang, Q. Q.; **Lim, H. S.** "Potential pharmacological chaperones targeting cancer-associated MCL-1 and Parkinson's disease-associated α-synuclein." *Proc. Natl. Acad. Sci. U.S.A.* **2014**, *111*, 11007.

DNA-Encoded Display of Chemical Libraries on Nanoparticles as a Versatile Selection Tool for Discovering Protein Ligands

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Abstract

DNA-encoded libraries (DELs) have emerged as a powerful tool for rapid discovering potent ligands for biological targets. However, current DEL technology is constrained by inherent limitations arising from the insolubility of DNA in organic solvents and instability of DNA under various chemical reaction conditions, which restricts the reactivity scope and structural diversity in library synthesis. Here, we have developed a new strategy called nanoDEL, where library molecules and DNA tags are displayed on the surface of nanoparticles. Since nanoparticles are dispersed well 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 aqueous reaction conditions. Importantly nanoDEL enables the execution of air-sensitive reactions requiring rigorously anhydrous conditions, which cannot be achieved by conventional DEL methods that rely on aqueous conditions. Notably, in our nanoDEL, multiple copies of a DNA tag with the same sequence are attached to an individual nanoparticle to encode a single compound. This feature enables nanoDEL to exhibit a considerably higher tolerance to DNA-damaging conditions compared to conventional DEL. For example, even under conditions that cause damage to the majority of the DNA, sequence analysis remains feasible by amplifying the remaining DNA tags on a nanoparticle. Consequently, nanoDEL facilitates the convenient utilization of existing organic reactions without the necessity to develop mild, DNA-compatible reactions. In addition, 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 stapled peptide inhibitors targeting a protein-protein interaction, exhibiting dissociation constants in the nanomolar range. Furthermore, we demonstrated that a large combinatorial encoded-library can be efficiently synthesized on nanoparticles using a synthetic scheme including moisture-sensitive reaction steps, which are not feasible with conventional DELs. Subsequently, through affinity selection of the nanoDEL, we successfully identified small molecule inhibitors targeting FAK *de novo*.

1. K. J. Lee, H. M. Wang, M. Kim, J. H. Park, J. Kim, S. Jang, D. Im, B. Goh, M. H. Shin, J. Shim, S. Kim, J Seo and **H. S. Lim*** "Encoded display of chemical libraries on nanoparticles as a versatile selection tool to discover protein ligands, *J. Am. Chem. Soc*. under revision.