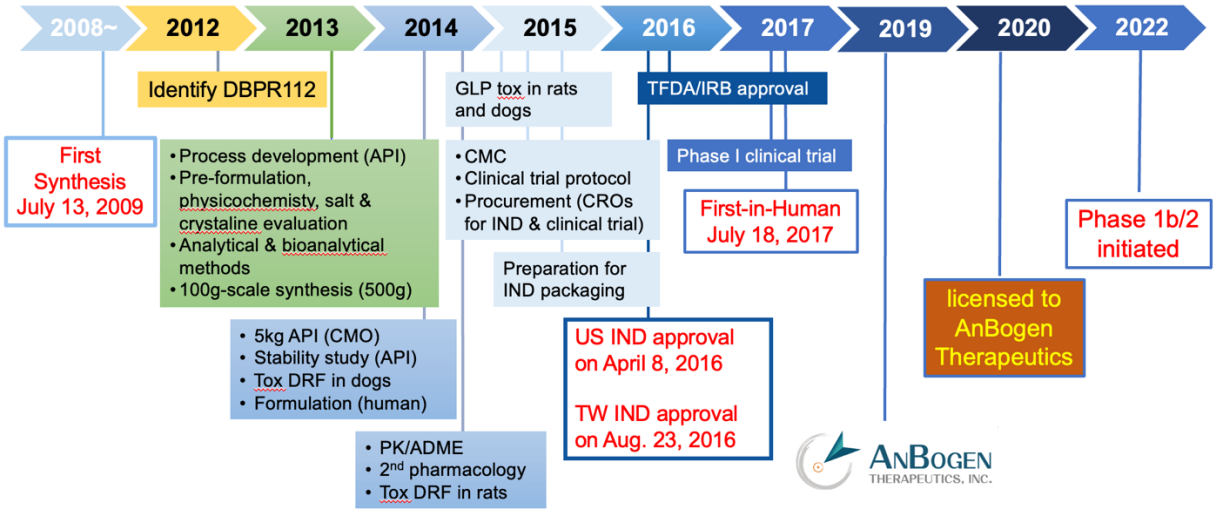
Translational Research and Spin-off: Novel Kinase Inhibitors from Bench to Clinic

實驗室到轉譯應用暨衍生新創: 新穎精準激酶抑制劑開發

Hsing-Pang Hsieh, Ph.D.
Director/ Distinguished Investigator
Institute of Biotechnology and Pharmaceutical Research
National Health Research Institutes, Miaoli County, Taiwan
hphsieh@nhri.edu.tw

Lung cancer is one of the chief causes of cancer death in the world; in addition, non-small cell lung cancer (NSCLC) accounts for 85% of the lung cancer deaths. The development of tyrosine kinase inhibitors (TKIs) targeting epidermal growth factor receptor (EGFR) have shown remarkable effects in patients but some acquired resistance after treatment. Therefore, the discovery of efficacious EGFR-TKIs poses an utmost priority.

Based on our achievement, we established a knowledge-based screening, followed by High Throughput Parallel Synthesis (HTPS) to synthesize more than 500 compounds. Further structure modification based on scaffold hopping approach by changing the pharmacophore moiety had led us to discover **DBPR112** as a potent EGFR-TKI clinical candidate showing excellent inhibitory ability on $EGFR^{L858R/T790M}$ and $EGFR^{exon20ins}$. **DBPR112** was orally effective against the growth of human lung H1975 tumors subcutaneously xenografted in nude mice. A dramatic reduction in tumor size was noted with **DBPR112** treatment, while displaying negligible body weight loss in all dosing groups. Furthermore, **DBPR112** was more tolerable than afatinib in mice. To date, all pre-clinical studies were completed, and the IND application of **DBPR112** was approved by US FDA and TW FDA in 2016. **DBPR112** was licensed to a new startup company, AnBogne Therapeutics in 2020. Currently, the Phase 1b/2 clinical trial has been undergoing in Taiwan.



References

1. Lin, S. Y.; Hsu Yung, C.; Peng, Y. H. ; Ke, Y. Y.; Lin, W. H.; Sun,H. Y.; Kuo, F. M.; Chen, P. Y.; Lien, T. W.; Chen, C. H.; Chu, C. Y.; Wang, S. Y.; Yeh, K. C.; Chen, C. P.; Hsu, J. TA; Wu, S. Y.; Yeh, T. K.; Chen, C. T.; **Hsieh, H. P.*** **J. Med. Chem.** 2019, 62, 10108-10123.
2. Li, M. C.; Coumar, M. ; Lin, . Y.; Lin, Y. S.; Huang, G. L.; Chen, C. H.; Lien, T. W.; Wu, Y. W.; Chen, Y. T.; Chen, C. P.; Huang, Y. C.; Yeh, K. C.; Yang, C. M.; Kalita, B.; Pan, S. L.; Hsu, T. A.; Yeh, T. K.; Chen, C. T.; **Hsieh, H. P.*** "Development of Furanopyrimidine-Based Orally Active Third-Generation EGFR Inhibitors for the Treatment of Non-Small Cell Lung Cancer" **J. Med. Chem.** 2023, **66**, 2566–2588.