26G-ISMS05

Search for Anti-leukemic Drugs Targeting the Transcription Factor Runx1 by INTENDD

○ Masaaki SHIINA[1], Shiho BABA[1], Akiko UCHIYAMA[1], Chikako OKADA[1], Takeshi TANAKA[2], Ken IKEDA[2], Shigetsugu KAWAKITA[2], Takao MATSUZAKI[2], Hirotsugu KOMATSU[2], Masato HOSODA[2], Kazuhiro OGATA[1]

[1]Yokohama City University, Graduate School of Medicine, [2]Interprotein Corporation

Advance in the molecular targeted therapy has dramatically changed and improved a treatment of cancer. However, its narrow target spectrum and acquired drug resistance in tumors remain to be solved. These problems partly stem from the limited variation of the targeted molecules; almost all have been protein kinases. To settle the problems, a promising way is to develop drugs targeting proteins other than kinases. One of the potential targets is a transcription factor because its mutation is known to be frequently involved in cancer development. However, transcription factors do not have any enzymatic activity themselves, and thus the compounds necessarily target the molecular interactions involved, which is quite challenging. This may explain why few drugs targeting transcription factors have been available as long as we know.

Our present research goal is to develop anti-leukemic drugs targeting a transcription factor, Runx1. Runx1 is known as a master regulator of the blood cell development, and various mutations of Runx1 gene have frequently been found in acute myeloblastic leukemia (AML) patients, leading to belief that Runx1 is an assured drug target for AML. Because Runx1 binds target gene enhancers as a heterodimer with CBFβ to regulate transcription, the desired compounds are likely to target the interactions of Runx1 with DNA or CBFβ .

We started our challenge with a unique type of *in silico* screening, INTENDD, which was developed by INTEPROTEIN CORP. and stands for INTerprotein's Engine for New Drug Design. In this method, we eyeball a real 3D model produced by a 3D printer based on a protein structure to find a molecular pocket for small compounds. Then, *in silico* screening is performed just for the candidate pockets. With INTENDD, we found and picked up 167 and 142 compounds targeting Runx1-DNA and Runx1-CBFβ interactions, respectively. Then we evaluated the inhibitory activity of the found compounds against DNA binding of Runx1 using surface plasmon resonance (SPR). We had totally 49 positive compounds, 3 of which strongly inhibited DNA binding of Runx1 with IC_{50} below 1 μM. We have verified that some of the positive compounds bind to Runx1 with the comparable affinity (K_D: 0.01-10 μM range).