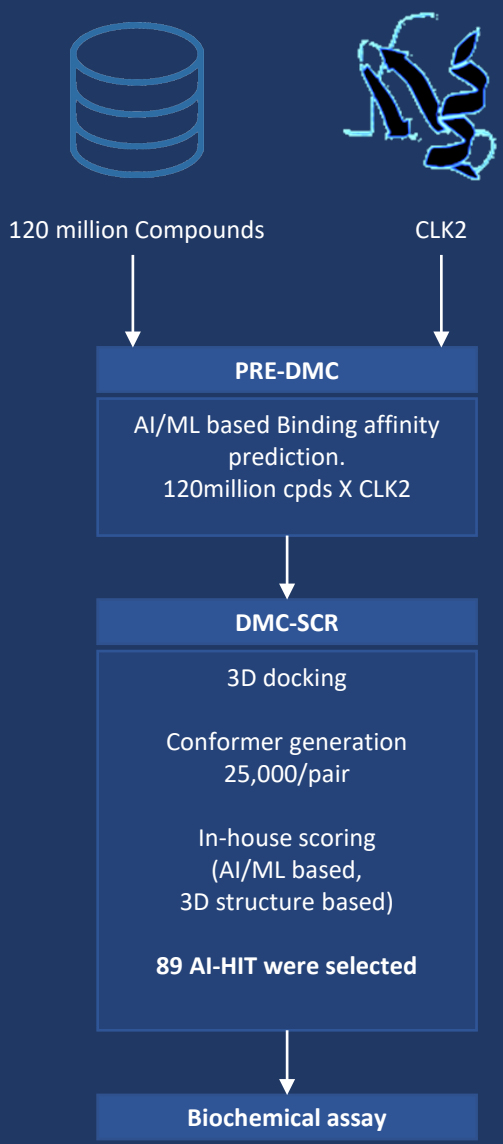
HIT DISCOVERY

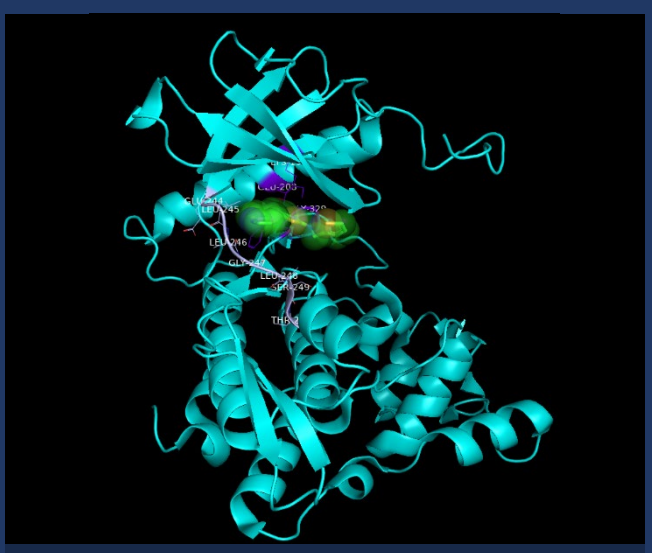
Discovering inhibitors with DeepMatcher® Platform

AI-based drug discovery platform “DeepMatcher®-Hit” conducts a comprehensive screening to find appropriate hit compounds using up to 1 billion compound library. The platform is fully automated and modulated into three parts for AI based 2D chemical screening, AI based 3D docking and Molecular docking simulation. Additionally, with our own high-performance computing infrastructure, DeepMatcher® has outstanding ability to predict binding pose of target protein and compound. Here we present case study of inhibitor screening to CLK2.

DeepMatcher® v1.8 screening



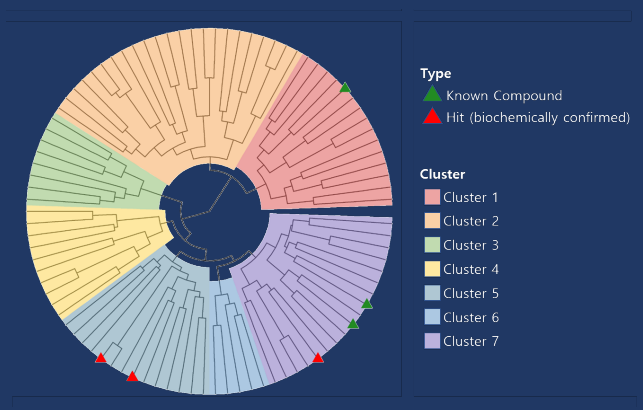
3D Structure of CLK2



CLK2, also known as CDC-like kinase 2, is a protein kinase that plays a role in the regulation of pre-mRNA splicing. Abnormalities in pre-mRNA splicing have been linked to various diseases, including cancer and neurodegenerative disorders. It has been found to promote the splicing of a variant of the CD44 gene that is associated with increased cancer cell motility and invasiveness.

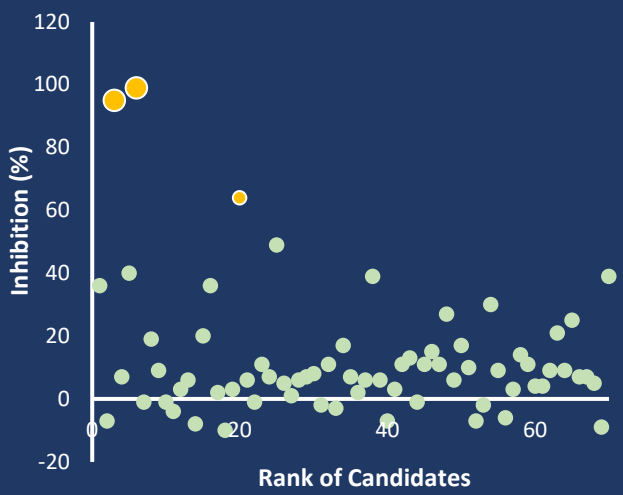
Structurally, CLK2 contains Kinase conserved hinge region from 244E to 250T and DFG motif from 327D to 328G. ATP binding related residue were known as 169L to 172G, 177V, 191A, 193K, 227V, 243F to 246L, 249S, 252D, 294E, 295N, 297L and 326V. (RCSB: 3NR9)

DeepMatcher® v1.8 AI-HIT analysis



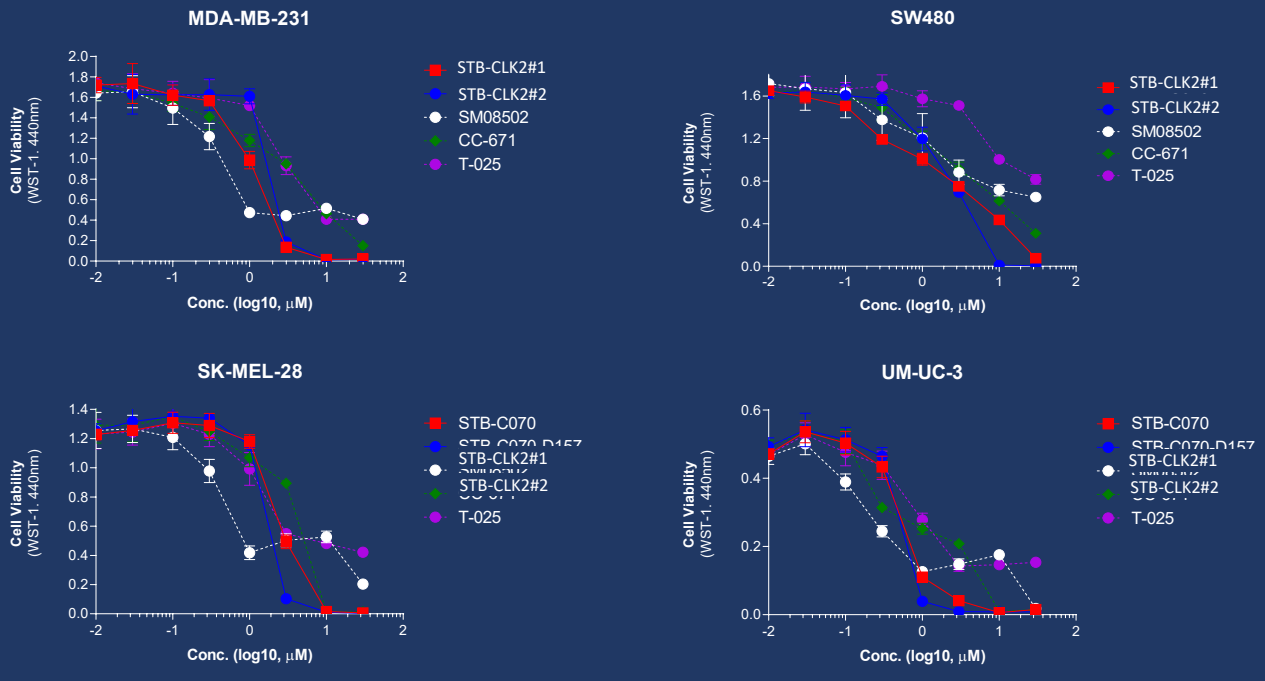
Deepmatcher® v1.8 provided 89 candidate as result of CLK2 inhibitor screening including three known compounds (Green arrowhead) which were not intentionally added. As a result of structure analysis using tanimoto coefficient with KNN algorithm, it was confirmed that 89 compounds were divided into 7 groups. Three known compounds were grouped into cluster 1 and 7. After biochemical assay, three compounds were identified as potential hit compounds (Red arrowhead). One of them were clustered into group 7 and two of them were clustered into group 5 with two known compounds.

Biochemical assay result of AI-Hits



Deepmatcher® v1.8 provided 89 candidate compounds with priority rank based on the in-house score. Purchasable compounds of the result were biochemically confirmed their inhibition activities. Three compounds of 74 purchased candidates (yellow circles) inhibited enzyme activity of CLK2 more than 50%. Additionally we confirmed all of 3 effective compounds were high ranked candidates which indicates that prediction of DeepMatcher® v1.8 was reliable.

Cell based assay result



STB-CLK2#1 and #2 were tested for their ability to inhibit cell growth against MDA-MB-231 (triple negative human breast adenocarcinoma), SE480 (human colon adenocarcinoma), SK-MEL-28 (melanoma) and UM-UC-3 (human transitional cell carcinoma of the bladder). In SW480 and UM-UC-3, both of compounds showed more potent inhibition activity compared with known inhibitors including SM08502, CC-671 and T-025. Currently, the two compounds are in the process of hit to lead optimization using our another platform DeepMatcher-Lead and preparing *in vivo* experiments.