Poster # C053

Acrivon Therapeutics' generative AI ensemble model (KaiSR) accurately predicts and expands proprietary, actionable kinase-substrate relationships globally for the human kinome

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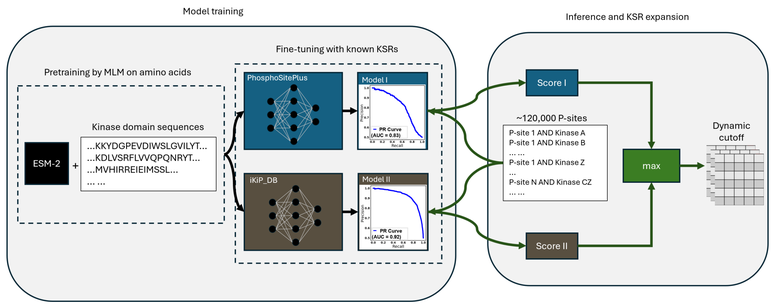
Background

- Protein phosphorylation, a post-translational modification regulated by protein kinases and phosphatases, plays a crucial role in controlling most aspects of biological processes.
- Understanding how the more than 500 human protein kinases selectively phosphorylate their specific substrates and contribute to disease-driving signaling pathways in the intact cell remain a critical challenge.
- The vast majority of phosphorylation sites from large-scale mass spectrometry-based phosphoproteomic datasets do not have responsible kinases assigned due to the lack of annotated kinase-substrate relationships (KSRs).
- Developing algorithms that can accurately expand KSRs for the human kinome has the potential to transform rational drug design and precision medicine by unbiased assessment of drug effects on the intact cellular signaling network.

Approach

- Acrivon Therapeutics has developed a proprietary generative AI KSR ensemble model ("KaiSR") for KSR prediction to enhance Acrivon Predictive Precision Proteomics (AP3) profiling, built from two transformer models fine-tuned on protein language model ESM-2.
- Fine-tuned model I, trained on KSRs from PhosphoSitePlus (PSP), achieved an area under the precision recall curve (AUPRC) of 0.83 on the hold-out dataset.
- Fine-tuned model II, trained on KSRs derived from the In Vitro Kinase-to-Phosphosite Database (iKiP-DB), achieved an AUPRC of 0.92 on the hold-out dataset.
- The KaiSR model is capable of zero-shot prediction, enabling accurate inference of KSRs across the entire human kinome.

Model architecture and performance

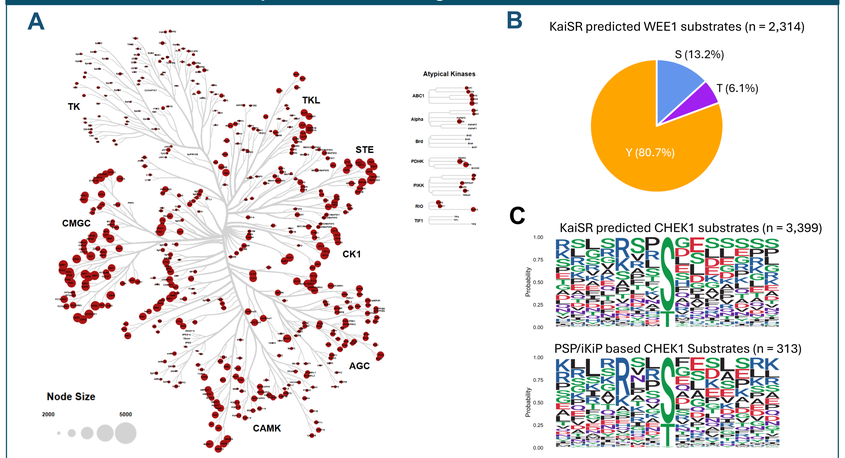


Model architecture of Acrivon Therapeutics' proprietary generative AI KSR prediction model "KaiSR"

Conclusion

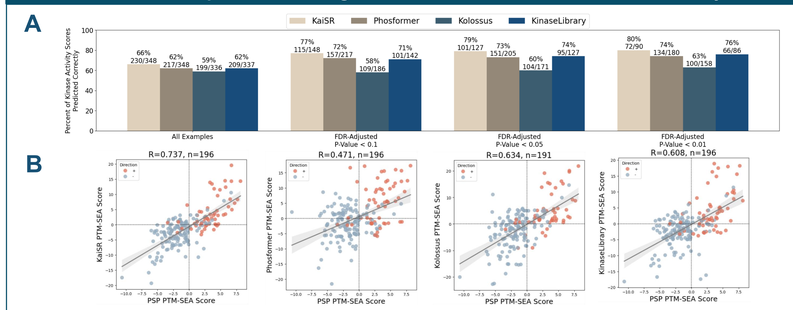
- KaiSR , Acrivon Therapeutics' proprietary generative AI KSR prediction model, accurately expands the KSR landscape across the entire human kinome.
- KaiSR outperforms existing generative AI or motif-based tools in predicting kinase activity inference.
- KaiSR provides unique, actionable insights into drug-regulated effects on kinome-wide kinase activity.
- The expanded KSR network generated by KaiSR enables a novel framework for target identification and prioritization.

KaiSR expands KSRs covering the entire human kinome



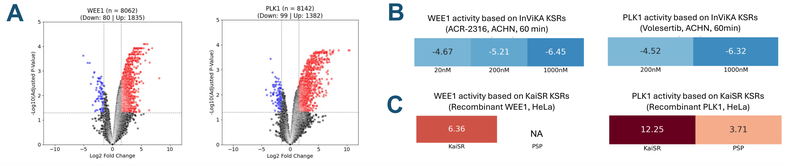
A) KaiSR-generated kinome-wide KSRs derived from 120,000 phosphosites identified in in-house phosphoproteomic experiments, with the node size representing the number of KSRs for the individual kinase; B) Example of zero-shot prediction illustrating WEE1 substrate identification; C) Sequence logo comparison of 15-mer peptide sequences centered on CHEK1 phosphosites predicted by KaiSR versus curated sites from PSP and iKiP-DB.

KaiSR outperforms other generative AI tools on inferred kinase activity



A) Comparison of correctly inferred kinase activities across different tools using a combined dataset from three publicly available drug perturbation studies; B) Correlation of PTM-SEA scores derived from PSP-based KSRs with scores generated from KSRs predicted by various tools.

Validating KaiSR predictions using in vitro kinase assay (InViKA)



Validating KaiSR predictions using in vitro kinase assay (InViKA) *cont.*

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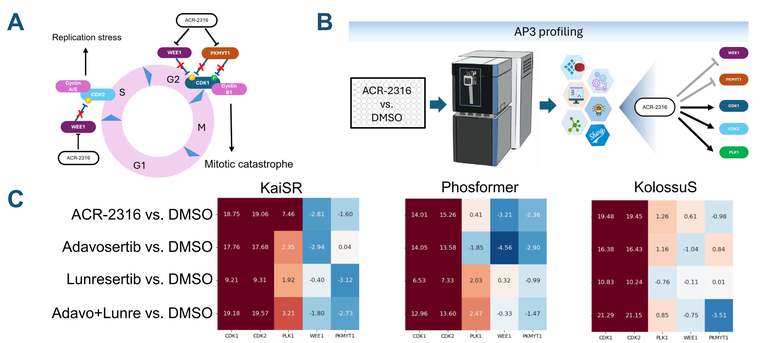
Kinase	LogFC Threshold	Adj.P Threshold	Sample Successes	Sample Size	Population Successes	Population Size	Hypergeometric P-Value	Odds Ratio
WEE1	3	0.05	16	87	117	4830	1.406087e-10	9.077645
PLK1	3	0.05	32	210	102	4811	6.346313e-20	8.299625

A) Volcano plots depicting regulated phosphosites induced separately by recombinant WEE1 and PLK1 kinases; B) Inferred kinase activity from in-house AP3 datasets using InViKA-informed KSRs; C) KaiSR-predicted KSRs reveal upregulation of kinase activity in each of the two InViKA experiments; D) Enrichment of KaiSR predicted substrates in the InViKA identified substrates

KaiSR differentiates ACR-2316 from other WEE1/PKMYT1 inhibitors

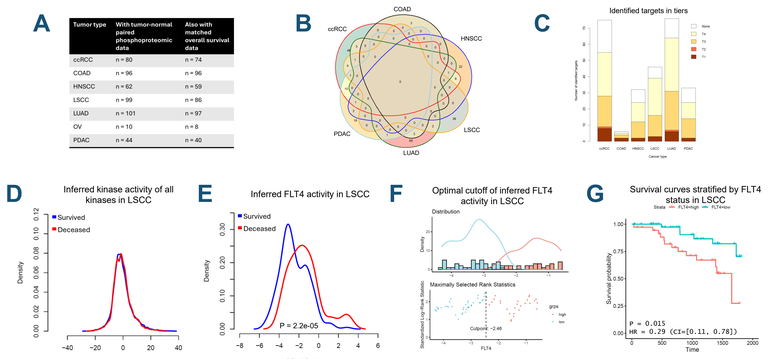


A) Mechanism of WEE1/PKMYT1 regulation of CDK1/CDK2 during the cell cycle; B) AP3 profiling demonstrates strong activation of CDK1, CDK2, and PLK1 by ACR-2316 using KSRs from PSP; C) Comparison of inferred kinase activities for five kinases across different drug treatments (200 nM, 60 min) and predicted by various generative AI tools.

KaiSR enabled target identification using real-world data

A

Tumor type	With tumor-normal paired phosphoproteomic data	Also with matched overall survival data
ccRCC	n = 80	n = 74
COAD	n = 96	n = 96
HNSCC	n = 62	n = 59
LSCC	n = 99	n = 86
LUAD	n = 101	n = 97
OV	n = 10	n = 8
PDAC	n = 44	n = 40



A) Patient numbers with paired tumor-normal phosphoproteomic data and matched overall survival data for each tumor type in CPTAC; B) Putative target identification based on relative kinase activity within each tumor type; C) Target stratification based on previously defined tier categories; D) Distribution of inferred kinase activity of all kinases in LSCC; E) Distribution of inferred kinase activity of FLT4, a top candidate target identified in LSCC; F) Optimal PTM-SEA score cutoff determination to distinguish survival probabilities between FLT4-high and FLT4-low patients in LSCC; G) Kaplan-Meier survival curves stratified by the cutoff determined in panel F.