Transcriptome-Based Drug Repositioning for T Cell Exhaustion: A Comparative Study of Manual Screening and AI-Assisted Candidate Prediction

GPT-5.1, Gemini 3 Pro and Claude Sonnet 4.5
(Names with versions only, sorted by priority)

First Author	**Second Author**	**Third Author**	**Fourth Author**
First Affiliation	Second Affiliation	Third Affiliation	Fourth Affiliation
First Address	Second Address	Third Address	Fourth Address
first@email	second@email	third@email	fourth@email

Abstract

T cell exhaustion is a major factor limiting the efficacy of immunotherapy in cancer and chronic infection. With progenitor exhausted $CD8^+$ T cells (Tpex) emerging as a key population that sustains proliferative immune responses after immune checkpoint blockade, strategies to modulate the Tpex transcriptional program have gained attention as a potential therapeutic avenue. Transcriptome-based drug repositioning via signature reversal enables *in silico* exploration of such targets; however, prior studies have largely relied on rule-based manual screening.

In this work, we reformulate drug repositioning for suppressing T cell exhaustion as a comparative problem between manual screening and AI-assisted candidate prediction. Using tumor-infiltrating $CD8^+$ T-cell single-cell RNA-seq data, we defined a Tpex-specific transcriptomic signature and leveraged LINCS L1000 perturbation profiles to identify compounds predicted to reverse the signature. We then compared an expert, rule-based pipeline against an AI-assisted prioritization pipeline. Manual screening identified 62 candidates, whereas the AI-assisted pipeline prioritized 121 candidates; three drugs (MK-2206, PF-562271, and PFI-1) were shared across both approaches, forming a conservative shortlist. These findings suggest that AI-based analysis can serve not only to automate conventional workflows but also as a hypothesis-generation "co-scientist" that expands the exploration space.

1 Introduction

In chronic infection and the tumor microenvironment, $CD8^+$ T cells exposed to persistent antigen stimulation can differentiate into a dysfunctional state known as T cell exhaustion, in which effector function and proliferative capacity are diminished. This state is accompanied by increased expression of inhibitory receptors such as PD-1, CTLA-4, and LAG3 and by characteristic transcriptomic remodeling, and it is considered a major contributor to the limited efficacy of cancer immunotherapy and to failure in controlling chronic infections.[Im et al., 2016, Utzschneider et al., 2016]

Within exhausted $CD8^+$ T-cell populations, a progenitor exhausted subset (Tpex) expressing *TCF7*, *LEF1*, and *BCL6* exhibits memory-like properties and retains self-renewal capacity. Prior studies have shown that Tpex cells are a primary source of proliferative immune responses after PD-1 blockade, motivating therapeutic strategies that aim to modulate the Tpex state rather than eliminate exhausted cells altogether.[Im et al., 2016, Miller et al., 2019]

Preprint. Under review.

In this context, transcriptome-based drug repositioning via signature reversal has attracted attention as an *in silico* strategy to identify candidate compounds—often with established safety profiles—that may modulate T cell exhaustion programs. In particular, the LINCS L1000 database provides large-scale, systematically measured drug-induced transcriptional perturbations, enabling transcriptome-guided screening and prioritization.[Ashburn and Thor, 2004, Lamb et al., 2006, Subramanian et al., 2017]

Nevertheless, prior studies have largely depended on rule-based manual screening, leaving candidate prioritization susceptible to analyst subjectivity. Although AI-based approaches may help mitigate these limitations, quantitative comparisons against manual analysis remain insufficient. Here, we compare transcriptome-based drug repositioning for suppressing T cell exhaustion using a manual screening pipeline and an AI-assisted candidate prediction pipeline under the same data setting. Using a Tpex-specific transcriptomic signature and the same perturbation resource, we systematically assess the contributions and limitations of each approach by analyzing their overlap and their method-specific candidates.

2 Method

2.1 Data acquisition and preprocessing

We used a publicly available single-cell RNA sequencing (scRNA-seq) dataset, GSE116390. This dataset consists of tumor-infiltrating $CD8^+$ T cells derived from the B16.F10 melanoma mouse model and includes both PMEL antigen-specific T cells and wild-type (WT) T cells. Raw count data were normalized to counts per 10,000 (CP10K) and log-transformed using $\log(x + 1)$. The same preprocessing pipeline was applied consistently across all subsequent analysis steps.

2.2 Tpex definition and differential expression analysis

To define progenitor exhausted T cells (Tpex) among tumor-infiltrating $CD8^+$ T cells, we used a signature-based approach. Based on prior studies, we selected 10 genes (*TCF7*, *LEF1*, *BCL6*, *SLAMF6*, *CXCR5*, *CCR7*, *IL7R*, *SELL*, *CD28*, *PDCD1*) as the Tpex signature.[Im et al., 2016, Miller et al., 2019] For each cell, the Tpex score was calculated as the mean of the log-normalized expression values of these genes, and only representative Tpex cells were retained for analysis.

Within the defined Tpex population, we conducted differential gene expression (DEG) analysis to characterize differences between PMEL antigen-specific and WT T cells. Genes with adjusted p-values < 0.05 and $|\log_2 \mathrm{FC}| \geq 0.1$ were defined as DEGs.

2.3 Transcriptome-based drug perturbation and candidate identification

The DEG signature was split into upregulated and downregulated gene sets. Using LINCS L1000 Level 4 perturbation profiles, we computed reversal scores for each drug with respect to the up- and down-signatures. We then integrated these scores into an integrated reversal score and ranked candidate drugs accordingly.

2.4 Comparison between manual screening and AI-assisted pipelines

Starting from the integrated reversal score, we applied a rule-based manual screening pipeline and an AI-assisted candidate prediction pipeline. In manual screening, candidates were filtered based on drug targets, mechanisms of action, and literature evidence linking the drug to T cell exhaustion. In the AI-assisted pipeline, candidates were prioritized by providing the problem definition and dataset description as prompts, without imposing explicit hand-crafted rules. We compared the candidate sets from both approaches to identify shared candidates and approach-specific candidates.

2.5 Statistical analysis and implementation environment

For DEG analysis, we used the Mann–Whitney U test and applied the Benjamini–Hochberg false discovery rate (FDR) procedure for multiple-hypothesis correction. All analyses were performed in Python 3.10 using Scanpy, NumPy, Pandas, and SciPy.[Wolf et al., 2018]

3 Results

3.1 Differential Gene Expression Landscape of Tpex Cells

We performed differential gene expression (DEG) analysis to characterize transcriptomic differences between PMEL-specific Tpex cells and WT Tpex cells. Figure 1 shows a volcano plot summarizing transcriptome-wide changes in PMEL Tpex relative to WT Tpex using $\log_2$ fold change and statistical significance ($-\log_{10}$ p-value). Applying the predefined thresholds (adj. p-value $<$ 0.05 and $|\log_2 \mathrm{FC}| \geq 0.1$), we identified 722 significantly upregulated genes and 506 significantly downregulated genes in PMEL Tpex. This DEG landscape forms the basis of the Tpex transcriptomic signature used for downstream drug-perturbation analyses.

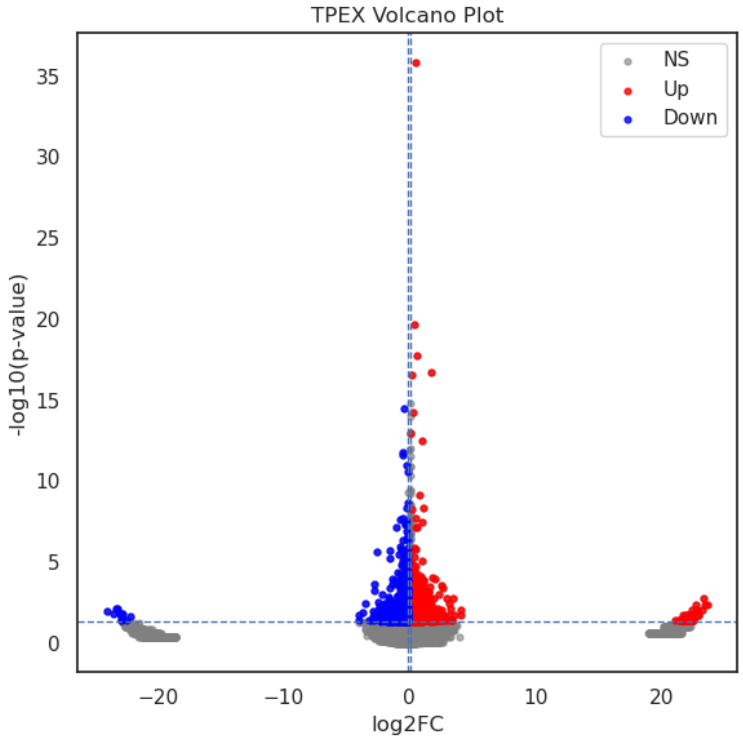

Figure 1: Volcano plot of differential gene expression in Tpex (WT vs Pmel). Each dot represents a gene, plotted by $\log_2$ fold change ($\log_2$FC; x-axis) and statistical significance ($-\log_{10}$ p-value; y-axis). Genes significantly upregulated in Pmel relative to WT ($\log_2$FC > 0.1, p < 0.05) are shown in red, while significantly downregulated genes ($\log_2$FC < -0.1, p < 0.05) are shown in blue. Genes that do not meet these thresholds are shown in gray. Vertical dashed lines indicate the $\log_2$FC cutoff (± 0.1), and the horizontal dashed line denotes the p-value significance threshold (p = 0.05).

3.2 Drug Candidates Identified by Manual and AI-Assisted Screening

Using the Tpex DEG signature, we performed signature-reversal analysis with LINCS L1000 Level 4 perturbation profiles and then applied manual screening and an AI-assisted pipeline to prioritize drug candidates. The AI-assisted pipeline prioritized 121 drug candidates, with top-ranked compounds frequently targeting HDAC, JAK, mTOR, GSK3, and other epigenetic regulators (Table 1). In contrast, the rule-based manual screening pipeline selected 62 candidates, with many compounds linked to kinase signaling, chromatin modification, and pathways such as TGF-β and MAPK (Table 2). While both approaches produced candidates predicted to reverse the Tpex transcriptomic signature, they differed in the breadth and composition of their hypothesis space: the AI-assisted approach covered a broader candidate space, whereas manual screening yielded a more conservative set.

Table 1: Top 10 drug candidates for Tpex modulation: AI-Assisted approach

AI-assisted Screening		
Drug Candidate	Target Gene	Mechanism of Action (MoA)
Chidamide	Hdac1	HDAC Inhibitor
Ruxolitinib	Jak1	JAK Inhibitor
Sirolimus (Rapamycin)	Mtor	mTOR Inhibitor
CHIR99021	Gsk3a	GSK3 Inhibitor
Tazemetostat	Ezh2	Epigenetic Inhibitor
Dasatinib	Src/Abl1/Kit	Src Inhibitor
M344	Hdac1	HDAC Inhibitor
Defactinib (VS-6063)	Ptk2	FAK/PTK2 Inhibitor
Vorinostat (SAHA)	Hdac1	HDAC Inhibitor
Baricitinib	Jak1	JAK Inhibitor

Table 2: Top 10 drug candidates for Tpex modulation: Conventional approach

Manual Screening		
Drug Candidate	Target Gene	Mechanism of Action (MoA)
XMD-892	NUAK1	NUAK1 Inhibitor
daminozide	PHF8	Histone Demethylase Inhibitor
I-BET-151	BTK	BTK Inhibitor
BMS-777607	AXL	AXL Inhibitor
SB-525334	TGFBR1	TGF-beta Receptor Inhibitor
tranylcypromine	MAOB	MAO-B Inhibitor
ALW-II-38-3	PDPK1	PDK1 Inhibitor
GSK-J2	KDM2B	Histone Demethylase Inhibitor
JQ1-(+)	BRD4	BET Bromodomain Inhibitor
FR-180204	MAPK1	ERK/MAPK Inhibitor

3.3 Overlap Between Manual and AI-Assisted Pipelines

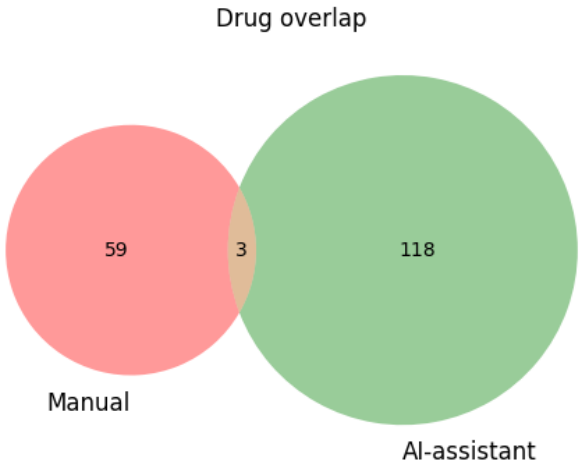

Figure 2: Drug overlap between manual and AI-assisted approaches based on integrated reversal scores. Venn diagram comparing drugs identified by manual and AI-assisted approaches using the L1000 Level 4 dataset. Integrated reversal scores were calculated based on Tpex upregulated and downregulated gene signatures. A total of 62 drugs were identified by the conventional approach and 121 drugs by the AI-assisted approach, with three drugs (PF-562271, PFI-1, and MK-2206) commonly identified by both methods.

Table 3: Common drug candidates identified by both approaches

Overlapping Candidates		
Drug Candidate	Target Gene	Mechanism of Action (MoA)
MK-2206	AKT1	AKT inhibitor
PF-562271	PTK2	FAK/PTK2 inhibitor
PFI-1	SETD7	BET bromodomain inhibitor

To assess overlap between the two pipelines, we examined the intersection of the shortlisted drug sets. Three drugs (MK-2206, PF-562271, and PFI-1) were identified by both approaches (Figure 2, Table 3). These shared candidates target AKT, FAK/PTK2, and BET bromodomain-associated mechanisms, respectively, and were consistently prioritized by two independent analytical strategies. Although the overlap proportion was limited relative to the total number of candidates, the shared set can be interpreted as a conservative shortlist reflecting convergent signals between manual analysis and AI-assisted prediction. Conversely, candidates unique to each approach may represent complementary hypotheses shaped by approach-specific search characteristics.

4 Discussion

In this study, we compared two analytical paradigms for transcriptome-based drug repositioning based on a Tpex transcriptomic signature: a rule-based manual screening approach and an AI-assisted candidate prediction approach. Although the two approaches shared a small set of common candidates, they showed clear differences in the size and composition of the resulting candidate sets. These differences should not be interpreted solely as a gap in "prediction performance"; rather, they likely reflect structural differences in search bias and hypothesis-generation mechanisms.

Manual screening has been widely used in transcriptome-based drug repositioning because it can integrate drug–target relationships, mechanisms of action, and literature evidence in an interpretable, stepwise manner. Such rule-based workflows have served as standard strategies in Connectivity Map and LINCS analyses and can be effective for rediscovering candidates along known biological pathways.[Lamb et al., 2006, Subramanian et al., 2017] However, this approach can be strongly constrained by the analyst's predefined hypothesis space, which creates a structural limitation for exploring novel mechanisms or indirect relationships.[Ashburn and Thor, 2004, Chen et al., 2016]

By contrast, the AI-assisted pipeline explored a broader candidate space by jointly interpreting transcriptome-based reversal scores and drug annotation information without fixing explicit mechanistic rules in advance. This characteristic is consistent with the notion that AI-based approaches are well suited for exploratory inference that leverages nonlinear relationships and latent patterns. Recent work in drug discovery and systems biology has suggested that AI may function not as a replacement for rule-based pipelines, but as a complementary tool that expands the exploration space and proposes additional hypotheses.[Stokes et al., 2020, Zhavoronkov et al., 2019]

The three shared candidates (MK-2206, PF-562271, and PFI-1) provide convergent evidence across two distinct prioritization logics. In transcriptome-based repositioning, such convergence signals can carry higher confidence than candidates obtained from a single pipeline and highlight the value of cross-validation via multiple analytical strategies.[Liberzon et al., 2015]

At the same time, the limited overlap relative to the total candidate pools indicates that the two approaches explore different hypothesis spaces even when using the same input data. Manual screening emphasizes consistency with established immunoregulatory and signaling pathways, whereas the AI-assisted approach can surface candidates with more diverse mechanisms and more indirect lines of evidence. This distinction supports the view that AI-based analysis can go beyond automating conventional workflows and can propose hypotheses that might not be considered a priori by human analysts.[King et al., 2009, Gil et al., 2014]

This perspective aligns with recent efforts to conceptualize AI not merely as a computational tool but as a "co-scientist" that participates in the scientific exploration process.[Jensen et al., 2014] In this framing, the value of AI-assisted analysis lies less in marginal improvements in ranking accuracy for

a single candidate and more in its ability to systematically propose exploration directions that can be connected to subsequent experimental design.

5 Limitations

This study has several limitations. First, all results are based on *in silico* transcriptomic analyses and do not include experimental validation. Second, language-model-based AI-assisted prioritization can be difficult to interpret mechanistically because the internal decision process is not fully transparent. Third, our interpretation of candidate overlap emphasizes analytical consistency rather than formal statistical testing of overlap or absolute comparisons of effect sizes.

6 Conclusion

Our main contribution is to provide a framework that directly compares AI-assisted candidate prediction against conventional manual screening for transcriptome-based drug repositioning targeting T cell exhaustion. This comparative strategy can serve as a reference point for quantitatively evaluating the roles and limitations of AI-based repositioning across disease areas.

7 References

Ted T. Ashburn and Karl B. Thor. Drug repositioning: identifying and developing new uses for existing drugs. *Nature Reviews Drug Discovery*, 3(8):673–683, 2004. doi: 10.1038/nrd1468.

Bin Chen, Lana Garmire, Diego F. Calvisi, Ming-Sound Tsao Chua, Robert K. Kelley, and Xin Chen. Harnessing big data for drug repositioning. *Briefings in Bioinformatics*, 17(6):1097–1105, 2016. doi: 10.1093/bib/bbv087.

Yolanda Gil, Mark Greaves, James Hendler, and Haym Hirsh. Amplify scientific discovery with artificial intelligence. *Science*, 346(6206):171–172, 2014. doi: 10.1126/science.1258040.

Seung-Jin Im, M. Hashimoto, Michael Y. Gerner, J. Lee, H. T. Kissick, M. C. Burger, Q. Shan, J. S. Hale, J. Lee, T. H. Nasti, A. H. Sharpe, G. J. Freeman, Ronald N. Germain, Hiroshi I. Nakaya, H.-H. Xue, and Rafi Ahmed. Defining CD8+ T cells that provide the proliferative burst after PD-1 therapy. *Nature*, 537(7620):417–421, 2016. doi: 10.1038/nature19330.

Peter B. Jensen, Lars J. Jensen, and Søren Brunak. Mining electronic health records: towards better research applications and clinical care. *Nature Reviews Genetics*, 15(3):171–182, 2014. doi: 10.1038/nrg3658.

Ross D. King, Jem Rowland, Stephen G. Oliver, Michael Young, Wayne Aubrey, Emma Byrne, Maria Liakata, Magnus Markham, Pinar Pir, Larisa N. Soldatova, Andrew Sparkes, Kenneth E. Whelan, and Amanda Clare. The automation of science. *Science*, 324(5923):85–89, 2009. doi: 10.1126/science.1165620.

Justin Lamb, Emily D. Crawford, David Peck, Joshua W. Modell, Irene C. Blat, Matthew J. Wrobel, Jim Lerner, Jean-Philippe Brunet, Aravind Subramanian, Kenneth N. Ross, Michael Reich, H. Hieronymus, Guo Wei, Scott A. Armstrong, Stephen J. Haggarty, Paul A. Clemons, L. Wei, Steven A. Carr, Eric S. Lander, and Todd R. Golub. The connectivity map: using gene-expression signatures to connect small molecules, genes, and disease. *Science*, 313(5795):1929–1935, 2006. doi: 10.1126/science.1132939.

Arthur Liberzon, Corey Birger, Helga Thorvaldsdóttir, Mahmoud Ghandi, Jill P. Mesirov, and Pablo Tamayo. The molecular signatures database (msigdb) hallmark gene set collection. *Cell Systems*, 1 (6):417–425, 2015. doi: 10.1016/j.cels.2015.12.004.

Brian C. Miller, Debashis R. Sen, R. Al Abosy, K. Bi, Y. V. Virkud, M. W. LaFleur, K. B. Yates, A. Lako, K. Felt, G. S. Naik, M. Manos, E. Gjini, J. R. Kuchroo, J. J. Ishizuka, J. L. Collier, J. W. Griffith, J. G. Doench, and W. N. Haining. Subsets of exhausted CD8+ T cells differentially mediate tumor control and respond to checkpoint blockade. *Nature*, 571(7766):540–544, 2019. doi: 10.1038/s41586-019-1342-0.

Jonathan M. Stokes, Kevin Yang, Kyle Swanson, Wei Jin, Alexandra Cubillos-Ruiz, Nicole M. Donghia, Connor R. MacNair, S. French, Luke A. Carfrae, Z. Bloom-Ackermann, Vivian M. Tran, Alexandra Chiappino-Pepe, Ahmed H. Badran, Ian W. Andrews, Eric J. Chory, George M. Church, Eric D. Brown, Tommi S. Jaakkola, Regina Barzilay, and James J. Collins. A deep learning approach to antibiotic discovery. *Cell*, 180(4):688–702.e13, 2020. doi: 10.1016/j.cell.2020.01.021.

Aravind Subramanian, Rajiv Narayan, Steven M. Corsello, David D. Peck, Ted E. Natoli, Xiaodong Lu, Joshua Gould, John F. Davis, Alina A. Tubelli, Jude K. Asiedu, David L. Lahr, Joel E. Hirschman, Zihan Liu, Michael Donahue, Bonnie Julian, Ma'ayan Khan, David Wadden, Ian C. Smith, Daniel Lam, Arthur Liberzon, Christie Toder, Mukta Bagul, Marek Orzechowski, Omayra M. Enache, F. Piccioni, Stacey A. Johnson, Nicholas J. Lyons, Andrea H. Berger, Alykhan F. Shamji, Angela N. Brooks, Anita Vrcic, Cory Flynn, Justine Rosains, Damian Y. Takeda, Ruisheng Hu, Donald Davison, Justin Lamb, Kristin Ardlie, Lisa Hogstrom, Peyton Greenside, Nathanael S. Gray, Paul A. Clemons, Stephen Silver, Xiaoyun Wu, W. Zhao, Will Read-Button, Xian Wu, Stephen J. Haggarty, Sachin Singh, and Todd R. Golub. A next generation connectivity map: L1000 platform and the first 1,000,000 profiles. *Cell*, 171(6):1437–1452.e17, 2017. doi: 10.1016/j.cell.2017.10.049.

Daniel T. Utzschneider, M. Charmoy, A. M. Mowat, and Dietmar Zehn. T cell factor 1-expressing memory-like CD8+ T cells sustain the immune response to chronic viral infections. *Immunity*, 45 (2):415–427, 2016. doi: 10.1016/j.immuni.2016.08.021.

F. Alexander Wolf, Philipp Angerer, and Fabian J. Theis. SCANPY: large-scale single-cell gene expression data analysis. *Genome Biology*, 19:15, 2018. doi: 10.1186/s13059-017-1382-0.

Alex Zhavoronkov, Yury A. Ivanenkov, Alexander Aliper, Mark S. Veselov, Vladimir A. Aladinskiy, Alexander Aliper, et al. Deep learning enables rapid identification of potent DDR1 kinase inhibitors. *Nature Biotechnology*, 37(9):1038–1040, 2019. doi: 10.1038/s41587-019-0224-x.

A Supplementary Information

Table S1: Drug candidates for Tpex modulation: AI-assisted approach

AI-assisted Screening		
Drug Candidate	Target Gene	Mechanism of Action (MoA)
Chidamide	Hdac1	HDAC Inhibitor
Ruxolitinib	Jak1	JAK Inhibitor
Sirolimus (Rapamycin)	Mtor	mTOR Inhibitor
CHIR99021	Gsk3a	GSK3 Inhibitor
Tazemetostat	Ezh2	EZH2 Inhibitor
Dasatinib	Src/Abl1/Kit	Multi-kinase Inhibitor
M344	Hdac1	HDAC Inhibitor
Defactinib (VS-6063)	Ptk2	FAK Inhibitor
Vorinostat (SAHA)	Hdac1	HDAC Inhibitor
Baricitinib	Jak1	JAK Inhibitor
TEW-7197 (Vactosertib)	Tgfbr1	TGF-beta Receptor Inhibitor
Everolimus	Mtor	mTOR Inhibitor
Temsirolimus	Mtor	mTOR Inhibitor
Ridaforolimus	Mtor	mTOR Inhibitor
PND-1186 (VS-4718)	Ptk2	FAK Inhibitor
Panobinostat	Hdac1	HDAC Inhibitor
Kenpaullone	Cdk1	CDK Inhibitor
TWS119	Gsk3b	GSK3 Inhibitor
GSK-LSD1 (GSK2879552)	Kdm1a	LSD1 Inhibitor
Romidepsin	Hdac1	HDAC Inhibitor
Belinostat	Hdac1	HDAC Inhibitor
Peficitinib	Jak1	JAK Inhibitor

Drug Candidate	Target Gene	Mechanism of Action (MoA)
INK128 (Sapanisertib)	Mtor	mTOR Inhibitor
EPZ-6438	Ezh2	EZH2 Inhibitor
AZD8055	Mtor	mTOR Inhibitor
Fedratinib	Jak2	JAK Inhibitor
Tofacitinib	Jak1	JAK Inhibitor
Copanlisib	Pik3ca	PI3K Inhibitor
LY2090314	Gsk3b	GSK3 Inhibitor
9-ING-41	Gsk3b	GSK3 Inhibitor
RepSox (E-616452)	Tgfbr1	TGF-beta Receptor Inhibitor
Abrocitinib	Jak1	JAK Inhibitor
Pacritinib	Jak2/Flt3	JAK/FLT3 Inhibitor
Upadacitinib	Jak1	JAK Inhibitor
Momelotinib	Jak1	JAK Inhibitor
Givinostat	Hdac1	HDAC Inhibitor
Filgotinib	Jak1	JAK Inhibitor
Idelalisib	Pik3cd	PI3K Inhibitor
Bosutinib	Src/Abl1	Src/ABL Inhibitor
Torin-2	Mtor	mTOR Inhibitor
Duvelisib	Pik3cd	PI3K Inhibitor
Alpelisib	Pik3ca	PI3K Inhibitor
Ibrutinib	Btk	BTK Inhibitor
Tideglusib	Gsk3b	GSK3 Inhibitor
Resminostat	Hdac1	HDAC Inhibitor
Trametinib	Map2k1	MEK Inhibitor
Axitinib	Flt1	VEGFR Inhibitor
Zanubrutinib	Btk	BTK Inhibitor
Decitabine	Dnmt1	DNMT Inhibitor
5-Azacitidine	Dnmt1	DNMT Inhibitor
OSI-027	Mtor	mTOR Inhibitor
CPI-1205	Ezh2	EZH2 Inhibitor
Entinostat	Hdac1	HDAC Inhibitor
AZD1080	Gsk3b	GSK3 Inhibitor
PP242	Mtor	mTOR Inhibitor
KX2-391 (Tirbanibulin)	Src	Src Inhibitor
Torin-1	Mtor	mTOR Inhibitor
Sunitinib	Pdgfra/Kit	Multi-kinase Inhibitor
Cobimetinib	Map2k1	MEK Inhibitor
Lenvatinib	Fgfr1/Ret	Multi-kinase Inhibitor
Acalabrutinib	Btk	BTK Inhibitor
Mocetinostat	Hdac1	HDAC Inhibitor
Abemaciclib	Cdk4	CDK4/6 Inhibitor
CPI-0610	Brd4	BET Bromodomain Inhibitor
ORY-1001 (Iadademstat)	Kdm1a	LSD1 Inhibitor
Afatinib	Egfr/Erbb2/Erbb4	Pan-HER Inhibitor
Ipatasertib	Akt1	AKT Inhibitor
Galunisertib (LY2157299)	Tgfbr1	TGF-beta Receptor Inhibitor
IN10018 (BI 885578)	Ptk2	FAK Inhibitor
GSK126	Ezh2	EZH2 Inhibitor
Ribociclib	Cdk4	CDK4/6 Inhibitor
Binimetinib	Map2k1	MEK Inhibitor
Selumetinib	Map2k1	MEK Inhibitor
Palbociclib	Cdk4	CDK4/6 Inhibitor
Dacomitinib	Egfr/Erbb2/Erbb4	Pan-HER Inhibitor
Erlotinib	Egfr	EGFR Inhibitor
Buparlisib (BKM120)	Pik3ca	PI3K Inhibitor
Dinaciclib	Cdk1	CDK Inhibitor
Saracatinib	Src	Src Inhibitor

Drug Candidate	Target Gene	Mechanism of Action (MoA)
MK-2206	Akt1	AKT Inhibitor
Pictilisib (GDC-0941)	Pik3ca	PI3K Inhibitor
RVX-208 (Apabetalone)	Brd2	BET Bromodomain Inhibitor
PF-562271	Ptk2/Ptk2b	FAK/Pyk2 Inhibitor
BI-853520	Ptk2	FAK Inhibitor
SB216763	Gsk3b	GSK3 Inhibitor
SB415286	Gsk3b	GSK3 Inhibitor
GSK2256098	Ptk2	FAK Inhibitor
ABBV-075 (Mivebresib)	Brd2	BET Bromodomain Inhibitor
PLX51107	Brd4	BET Bromodomain Inhibitor
Lapatinib	Egfr/Erbb2	EGFR/HER2 Inhibitor
Osimertinib	Egfr	EGFR Inhibitor
Neratinib	Egfr/Erbb2/Erbb4	Pan-HER Inhibitor
Gefitinib	Egfr	EGFR Inhibitor
OTX015 (Birabresib)	Brd2	BET Bromodomain Inhibitor
I-BET762 (Molibresib)	Brd2	BET Bromodomain Inhibitor
AZD5153	Brd4	BET Bromodomain Inhibitor
LY364947	Tgfbr1	TGF-beta Receptor Inhibitor
SD-208	Tgfbr1	TGF-beta Receptor Inhibitor
SB431542	Acvr1b	ALK4/5/7 Inhibitor
LY2109761	Tgfbr1	TGF-beta Receptor Inhibitor
GW788388	Tgfbr1	TGF-beta Receptor Inhibitor
Pelitinib	Egfr/Erbb2	EGFR/HER2 Inhibitor
Canertinib	Egfr/Erbb2	EGFR/HER2 Inhibitor
A83-01	Tgfbr1	TGF-beta Receptor Inhibitor
SB525334	Tgfbr1	TGF-beta Receptor Inhibitor
PF-573228	Ptk2	FAK Inhibitor
NVP-TAE226	Ptk2/Igf1r	FAK/IGF1R Inhibitor
TAE226	Ptk2	FAK Inhibitor
Alvocidib (Flavopiridol)	Cdk1	CDK Inhibitor
JQ1	Brd2	BET Bromodomain Inhibitor
PP2	Src	Src Inhibitor
Wortmannin	Pik3ca	PI3K Inhibitor
AZD5438	Cdk1	CDK Inhibitor
PFI-1	Brd4	BET Bromodomain Inhibitor
I-BET151	Brd2	BET Bromodomain Inhibitor
Roscovitine (Seliciclib)	Cdk2	CDK Inhibitor
THZ1	Cdk7	CDK7 Inhibitor
Y15	Ptk2	FAK Inhibitor
AG-1478	Egfr	EGFR Inhibitor
LY294002	Pik3ca	PI3K Inhibitor
THZ531	Cdk12	CDK12/13 Inhibitor

Table S2: Drug candidates for Tpex modulation: Conventional approach

Manual Screening		
Drug Candidate	Target Gene	Mechanism of Action (MoA)
XMD-892	NUAK1	NUAK1 Inhibitor
daminozide	PHF8	Histone Demethylase Inhibitor
I-BET-151	BTK	BTK Inhibitor
BMS-777607	AXL	AXL Inhibitor
SB-525334	TGFBR1	TGF-β Receptor Inhibitor
tranylcypromine	MAOB	MAO-B Inhibitor
ALW-II-38-3	PDPK1	PDK1 Inhibitor

Drug Candidate	Target Gene	Mechanism of Action (MoA)
GSK-J2	KDM2B	Histone Demethylase Inhibitor
JQ1-(+)	BRD4	BET Bromodomain Inhibitor
FR-180204	MAPK1	ERK/MAPK Inhibitor
trametinib	MAP2K1	MEK Inhibitor
PFI-1	SETD7	Histone Methyltransferase Inhibitor
SB-239063	MAPK9	JNK Inhibitor
ACY-1215	HDAC6	HDAC Inhibitor
tie2-kinase-inhibitor	TEK	Tie2 Kinase Inhibitor
regorafenib	EPHX2	Epoxide Hydrolase Inhibitor
alpelisib	PIK3CA	PI3K Inhibitor
KI-20227	CSF1R	CSF1R Inhibitor
fostamatinib	SYK	SYK Inhibitor
GNF-2	ABL1	ABL Inhibitor
PF-04217903	MET	MET Inhibitor
SGX523	MET	MET Inhibitor
RAF-265	BRAF	BRAF Inhibitor
saracatinib	PKMYT1	WEE1/PKMYT1 Inhibitor
rucaparib	PARP2	PARP Inhibitor
barasertib-HQPA	AURKB	Aurora Kinase Inhibitor
dabrafenib	BRAF	BRAF Inhibitor
WZ-4-145	CXCR4	CXCR4 Antagonist
PLX-4720	RAF1	RAF Inhibitor
CC-401	DYRK1A	DYRK Inhibitor
CYT387	TBK1	TBK1 Inhibitor
MK-2206	AKT1	AKT Inhibitor
GSK-1059615	KDM2B	Histone Demethylase Inhibitor
BX-795	MARK4	MARK4 Inhibitor
foretinib	MET	MET Inhibitor
dacomitinib	EGFR	EGFR Inhibitor
THZ-2-98-01	PTPN11	SHP2 Inhibitor
crizotinib	MET	MET Inhibitor
NU-7026	PRKDC	DNA-PK Inhibitor
MC1568	HDAC6	HDAC Inhibitor
enzastaurin	PRKCB	PKC Inhibitor
PF-562271	PTK2	FAK Inhibitor
GSK-1904529A	KDM2B	Histone Demethylase Inhibitor
PF-431396	PTK2	FAK Inhibitor
CP-724714	EGFR	EGFR Inhibitor
BS-181	CCNH	CDK-activating Kinase Inhibitor
canertinib	EGFR	EGFR Inhibitor
ischemin	TP53	p53 Modulator
vemurafenib	ARAF	RAF Inhibitor
rebastinib	ABL1	ABL Inhibitor
afatinib	EGFR	EGFR Inhibitor
PHA-665752	MET	MET Inhibitor
KIN001-043	HDAC1	HDAC Inhibitor
nintedanib	KDR	VEGFR Inhibitor
PHA-767491	CDK7	CDK7 Inhibitor
mocetinostat	HDAC1	HDAC Inhibitor
JNK-IN-5A	MAPK10	JNK Inhibitor
rigosertib	PLK1	PLK1 Inhibitor
AZD-5438	CDK2	CDK Inhibitor
PHA-793887	CDK5	CDK Inhibitor
CGP-60474	CCNE1	CDK/Cyclin Inhibitor
dinaciclib	CDK5	CDK Inhibitor

AI Co-Scientist Challenge Korea Paper Checklist

1. **Claims**

   Question: Do the main claims made in the abstract and introduction accurately reflect the paper's contributions and scope?

   Answer: [Yes]

   Justification: The abstract and introduction claim a comparative evaluation of manual screening vs. AI-assisted candidate prioritization using the same Tpex signature and LINCS L1000 data, which matches the described methods and reported results.

2. **Limitations**

   Question: Does the paper discuss the limitations of the work performed by the authors?

   Answer: [Yes]

   Justification: The paper includes a dedicated Limitations section stating that the study is *in silico* only, noting interpretability limits of AI-assisted prioritization, and clarifying the interpretation of overlap.

3. **Theory Assumptions and Proofs**

   Question: For each theoretical result, does the paper provide the full set of assumptions and a complete (and correct) proof?

   Answer: [N/A]

   Justification: The paper does not present new theoretical results or formal proofs; it reports a transcriptome-based screening and comparison study.

4. **Experimental Result Reproducibility**

   Question: Does the paper fully disclose all the information needed to reproduce the main experimental results of the paper to the extent that it affects the main claims and/or conclusions of the paper (regardless of whether the code and data are provided or not)?

   Answer: [Yes]

   Justification: The dataset (GSE116390), preprocessing (CP10K + $\log(x+1)$), Tpex marker set, DEG thresholds, and use of LINCS L1000 Level 4 signature reversal are specified to support reproducing the main workflow.

5. **Open access to data and code**

   Question: Does the paper provide open access to the data and code, with sufficient instructions to faithfully reproduce the main experimental results, as described in supplemental material?

   Answer: [No]

   Justification: The study uses public datasets (e.g., GEO and LINCS), but the full analysis code and a complete reproduction package are not provided in this submission.

6. **Experimental Setting/Details**

   Question: Does the paper specify all the training and test details (e.g., data splits, hyperparameters, how they were chosen, type of optimizer, etc.) necessary to understand the results?

   Answer: [N/A]

   Justification: The work does not involve training models with train/test splits or optimizers; it performs DEG analysis, signature reversal scoring, and candidate ranking.

7. **Experiment Statistical Significance**

   Question: Does the paper report error bars suitably and correctly defined or other appropriate information about the statistical significance of the experiments?

   Answer: [Yes]

   Justification: Statistical significance is reported for DEG analysis via Mann–Whitney U testing with Benjamini–Hochberg FDR correction and explicit thresholds.

8. **Experiments Compute Resources**

   Question: For each experiment, does the paper provide sufficient information on the computer resources (type of compute workers, memory, time of execution) needed to reproduce the experiments?

   Answer: [No]

   Justification: The software environment is described, but hardware, memory, and runtime requirements are not reported.

9. **Code Of Ethics**

   Question: Does the research conducted in the paper conform, in every respect, with the NeurIPS Code of Ethics?

   Answer: [Yes]

   Justification: The study analyzes publicly available transcriptomic datasets and reports *in silico* results without conducting human-subject experiments or collecting sensitive personal data.

10. **Broader Impacts**

    Question: Does the paper discuss both potential positive societal impacts and negative societal impacts of the work performed?

    Answer: [No]

    Justification: The manuscript focuses on methodological comparison and does not include an explicit broader-impacts discussion of potential benefits and risks.

11. **Safeguards**

    Question: Does the paper describe safeguards that have been put in place for responsible release of data or models that have a high risk for misuse?

    Answer: [N/A]

    Justification: The paper does not release high-risk generative models or new sensitive datasets; it analyzes public resources and reports ranked hypotheses.

12. **Licenses for existing assets**

    Question: Are the creators or original owners of assets (e.g., code, data, models), used in the paper, properly credited and are the license and terms of use explicitly mentioned and properly respected?

    Answer: [No]

    Justification: Primary sources for public datasets and tools are cited, but the licenses/terms of use for each asset are not explicitly listed.

13. **New Assets**

    Question: Are new assets introduced in the paper well documented and is the documentation provided alongside the assets?

    Answer: [N/A]

    Justification: The paper does not introduce or release new datasets, code packages, or pretrained models as standalone assets.

14. **Crowdsourcing and Research with Human Subjects**

    Question: For crowdsourcing experiments and research with human subjects, does the paper include the full text of instructions given to participants and screenshots, if applicable, as well as details about compensation (if any)?

    Answer: [N/A]

    Justification: The study does not involve crowdsourcing or research with human subjects.

15. **Institutional Review Board (IRB) Approvals or Equivalent for Research with Human Subjects**

Question: Does the paper describe potential risks incurred by study participants, whether such risks were disclosed to the subjects, and whether Institutional Review Board (IRB) approvals (or an equivalent approval/review based on the requirements of your country or institution) were obtained?

Answer: [N/A]

Justification: No human-subject research is conducted; therefore, IRB approval is not applicable.