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Supplemental information

Chemical-induced gene expression ranking and its application to pancreatic cancer drug repurposing

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Supplemental Notes

Supplemental Note 1: Random Ranking Method

The random ranking method can be seen as the random permutation over the gene sequence. Thus, its performances measured by Precision@K can be computed theoretically. In particular, Precision@K returned by the random ranking method can be seen as the random variable $X = Y/K$ where Y follows the hypergeometric distribution $f(y|A, N, n)$ with $A = K$ is the number of top-K regulated genes, $N = n_g$ is the number of genes, and $n = K$ is number of top regulated genes in predicted profiles used to compute Precision@K. Then the average performance of the random ranking method measured by Precision@K is computed as $\bar{X} = \frac{\bar{Y}}{K} = \frac{nA}{NK} = \frac{K}{n_g}$. For measuring performances by NDCG we run random ranking method 100 times for each gene expression profile and return the average results.

Supplemental Note 2: Details of Data-driven Graph-based Fingerprint (Neural Fingerprint)

The pseudo-code of data-driven graph-based fingerprint generated by graph convolutional network is shown in Algorithm 1. In general, graph convolutional network updates the representation of one particular nodes from information of its neighborhoods in the graph by convolutional operation so each node in the output layer represents the sub-structure of the original graph. Follow the setting in [1], we use the 2-layer graph convolutional network (radius = 2) which means that the sub-structures represented by this method are the span of 2-hop distance from the atom. Inputs for graph convolutional network are the feature vectors of atoms and bonds that captures their properties such as atom symbol, degree, and type of bonds. The dimension of fingerprints generated by graph convolutional network is set to be 1024 which is similar to ECFP for a fair comparison.

Supplemental Note 3: Learning-to-rank Objective Functions

CIGER treats the gene expression profiles as the lists ranked by their z-score values and then minimizes several learning-to-rank objective functions including both pair-wise (i.e. RankNet) and list-wise (i.e. ListNet, ListMLE, and RankCosine) functions between the predicted ($\mathbf{Y}$) and the ground-truth ($\mathbf{Z}$) gene expression profiles. The details of these learning-to-rank objective functions are presented in the following paragraphs.

ListNet. [2] is the list-wise ranking objective function that minimizes the cross-entropy loss between top-1 probability of the predicted and ground-truth gene expression profiles. In particular, the top-1 probability of gene i in the gene expression profile j is the probability of that gene being ranked first among all genes in that profile and is computed as follows:

$$P_{top-1}^{z^{(j)}}(x_i^{(j)}) = \frac{\exp(z_i^{(j)})}{\sum_{k=1}^{n_g} \exp(z_k^{(j)})}$$

Algorithm 1: Pseudo-code of data-driven graph-based fingerprint

Input: Chemical graph $= (V, E)$, radius R, hidden weights $(\mathbf{H}_1^1, ..., \mathbf{H}_R^5), (\mathbf{U}_1, ..., \mathbf{U}_l), (\mathbf{W}_1, ..., \mathbf{W}_l)$

Output: Neural fingerprint $\mathbf{f}$

for $l = 1$ *to* R **do**

  for $i = 1$ *to* $|V|$ **do**

    $V_{neighbor}, E_{neighbor} \leftarrow Neighbors(\mathbf{v}^{(i)})$;

    $\mathbf{v}_l^{(i)} \leftarrow \sum_{\mathbf{v}^{(j)} \in V_{neighbor}} \mathbf{v}_{l-1}^{(j)}$;

    $\mathbf{e}_l^{(i)} \leftarrow \sum_{\mathbf{e}^{(j)} \in E_{neighbor}} \mathbf{e}_0^{(j)}$;

    $\mathbf{v}_l^{(i)} \leftarrow concat(\mathbf{v}_l^{(i)}, \mathbf{e}_l^{(i)})$;

    $\mathbf{v}_l^{(i)} \leftarrow ReLU(\mathbf{v}_{l-1}^{(i)}\mathbf{U}_l + (\mathbf{v}_l^{(i)}\mathbf{W}_l)$;

    $\mathbf{v}_l^{(i)} \leftarrow softmax(\mathbf{v}_l^{(i)}\mathbf{H}_l^{|V_{neighbor}|})$;

    $\mathbf{f} \leftarrow \mathbf{f} + \mathbf{v}_l^{(i)}$;

  end

end

and then ListNet minimizes the loss:

$$L_{ListNet} = -\sum_{j=1}^{n_b}\sum_{k=1}^{n_g} P_{top-1}^{z^{(j)}}(x_i^{(j)}) \log(P_{top-1}^{y^{(j)}}(x_i^{(j)}))$$

ListMLE. [3] is the list-wise ranking objective function that maximizes the likelihood of the rank given the list of gene expression values. In particular, let $\pi^{(j)}$ is the ranked list given the gene expression profile $\mathbf{z}^{(j)}$, the negative log-likelihood of the ranked lists is computed as follows:

$$L_{ListMLE} = -\sum_{j=1}^{n_b}\sum_{i=1}^{n_g} \frac{\exp(y_{\pi_i^{(j)}}^{(j)})}{\sum_{k=i}^{n_g} \exp(y_{\pi_k^{(j)}}^{(j)})}$$

RankCosine. [4] is the list-wise ranking objective function that measures the cosine similarity between the predicted and ground-truth ranking lists. In particular, this score is computed as follows:

$$L_{RankCosine} = \frac{1}{2}\sum_{j=1}^{n_b}\left(1 - \frac{\mathbf{z}^{(j)T}\mathbf{y}^{(j)}}{\left\|\mathbf{z}^{(j)}\right\|\left\|\mathbf{y}^{(j)}\right\|}\right)$$

RankNet. [5] is the pair-wise ranking objective function that considers the ranking between every pairs of genes. In particular, given the ranked list $\pi^{(j)}$ of gene expression profiles $\mathbf{z}^{(j)}$, RankNet is computed as the cross-entropy loss between predicted and ground-truth pair-wise ranked probabilities as follows:

$$L_{RankNet} = \sum_{j=1}^{n_b}\sum_{i,k=1}^{n_g} -\hat{P}_{ik}^{(j)} \log(P_{ik}^{(j)}) - (1 - \hat{P}_{ik}^{(j)}) \log(1 - P_{ik}^{(j)})$$

where $\hat{P}_{ik}^{(j)}$ and $P_{ik}^{(j)}$ are the ground-truth and predicted probabilities that gene i is ranked higher than gene k and are computed as follows:

$$\hat{P}_{ik}^{(j)} = \frac{1}{2}(1 + S_{ik}^{(j)})$$

$$P_{ik}^{(j)} = \frac{1}{1 + exp(-(y_i^{(j)} - y_k^{(j)}))}$$

where $S_{ik}^{(j)} = 1$ if gene i is ranked higher than gene k in the ranked list $\pi^{(j)}$, -1 if gene k is ranked higher, and 0.5 if they are ranked equally.

Supplemental Note 4: Details of Methods for Experimental Validation

Cell Culture

PANC-1 and PSN-1 cells were obtained from ATCC. Cells were cultured in complete Dulbecco's Modified Eagle Medium (DMEM) (Gibco, Cat No.21969-035 USA) with 10% Fetal Bovine Serum (FBS), 2mM L-Glutamine (Gibco, USA) and 50u/ml penicillin/streptomycin (Gibco, ref 15140-122, USA). Cells were cultured at 37°C with 5% CO_2 in a humidified incubator. To harvest cells, media was removed, and cells were washed with PBS and trypsinised with 2-4 ml trypsin (Gibco, Cat No. 25200-056, USA) and incubated for 4 minutes to detach. Trypsin was then neutralised by adding 8-10 ml complete media and cells were collected and counted using countess (C10283 Fisher Scientific, Rockford, IL, USA) following manufacturer's protocol.

Drugs and Reagents

Drugs for Treatment. Drugs used with their stock and working concentrations are summarised in Supplemental Table S7.

Antibody and Enzymes. Antibodies, enzymes used in western blot and dot blot are summarised in Supplemental Table S8. TET2 and GATA6 primary antibodies were obtained from Abcam (Cambridge, UK) and used at dilution of 1:500. 5hmc was obtained from Active motif (California, USA) and used at dilution 1:1000. Beta-actin was obtained from Proteintech (USA) and used at 1:1000. Anti-ribbit HRP (7074S, Cell Signalling Technology Danvers, USA) and anti-mouse HRP (7076S, Cell Signalling Technology Danvers, USA) were used at dilution of 1:5000. RNA A (EN0531, Thermo Scientific, Waltham, USA), used at concentration of 200 μg/ml/1x106 cells based on previous study [6].

Buffer and Solution. Buffer and solution used are summarised in Supplemental Table S9. NuPAGE Sample buffer (NP008, Thermo Scientific, Waltham, USA) and NuPAGE running buffer (NP0001-02, Thermo Scientific, Waltham, USA) were used for western blot. Transfer buffer, lysis buffer, denaturing buffer and TBST were prepared as described [7]. Transfer buffer was prepared as 10x stock solution containing 144g Glycine, 30.2g tris base. Lysis buffer contained 100mM

Tris-HCL [pH8.5], 5mM EDTA, 0.2% SDS, 100mM NaCL, 0.5mg/ml Proteinase K, denaturing buffer was made up of 200mM NaOH, 20mM EDTA and TBS-0.1% Tween 20 was made with 6.05 Tris 8.76g NaCl, pH 7.6, with 0.1% Tween 20 (Acros Organics Cat No. 233360010, BVBA, Geel, Belgium). Ripa Buffer (Ref 89900 Thermo Scientific, Waltham, USA) included protease inhibitor (Ref 04693116001, Roche, Basel, Switzerland) and phosphate inhibitor (Ref A32957, Pierce, Thermo Scientific, Waltham, USA).

Protein Isolation and Western Blotting

Protein Isolation and Normalisation. Protein isolation was performed as described published [7]. Briefly, cells are harvested and washed twice in cold PBS. PBS was removed by spinning at 350 rpm for 5 minutes and for every 1,000,000 cells 100 μl Ripa Buffer supplemented with protease inhibitor (Ref 04693116001, Roche, Basel, Switzerland) and phosphate inhibitor (Ref A32957 Pierce Thermo Scientific, Waltham, USA) (as described in Supplemental Table S8) was added and cells were lysed for 15 minutes while rotating at 4°C . Samples were then spined at 13000 rpm for 10 minutes and protein lysate was collected. Lysate obtained was quantified using BCA kit (Ref 23225, Thermo Scientific, Waltham, USA) with albumin standard (Ref 23209 Thermo Scientific, Waltham, USA) in 96-well flat bottom plates (Geriner Bio-one Ref. 655080) following manufacturer's protocol. Results were read and analysed using POLARstar Omega Plate Reader and protein was normalised.

Western Blot. Western blots were performed and analysed as published [7]. Briefly, lysate containing 50 μg protein was mixed with 4X NuPAGE LDS Sample Buffer (NP0008, Thermo Scientific, Waltham, USA) with 1 mM DTT and boiled at 95°C for 5 minutes. Samples were run on 4%-12% NuPAGE Bis-Tris gels (Cat. No NP0335BOX, Thermo Scientific, Waltham, USA) in 1X NuPAGE MOPS SDS Running Buffer (NP0001-02, Thermo Scientific, Waltham, USA) for 100 minutes at 150 V. Proteins were then transferred onto Polyvinylidene Difluoride (PVDF) membranes (IPVH00010, Sigma, St Louis, MO, USA) in transfer buffer (Described in Supplemental Table S8). PVDF membranes were activated in 100% methanol 10 minutes before transfer and methanol was washed off and replaced with transfer buffer. Proteins were then transferred in transfer buffer for 90 minutes at 100V. Membrane was checked using Ponceau S staining (P7170-1L, Sigma, St Louis, MO, USA) by incubating in 3ml Ponceau S staining, followed by 3 x 5 minutes wash. Membranes were then blocked using 3% milk in TBS with 0.1% Tween20 (TBST) for 1 hour. Primary antibody (As described in Supplemental Table S8) was then diluted in 3% milk in TBST, and membranes were cut and incubated in corresponding antibody overnight at 4°C. Membranes were then washed 3 x 10-15 minutes in TBST and incubated in secondary antibody (As describe in Supplemental Table S8) at 1:5000 in 3% milk and TBST for 1 hour at room temperature followed by 3 x 10-15 minutes wash in TBST. To develop, membranes were incubated in enhanced chemiluminescence kits (ECL) (Millipore, Burlington, MA, USA) for

1 minute. Excess substrate was drained off and signals were immediately developed using CL-Xposure film (Ref 34089 Thermo Scientific, Waltham, USA) with X-ray film processer (Ecomax 1186-3-4000) and detected using Chemidoc MP (Bio-Rad Laboratories, Hercules, CA, USA). For Chemidoc MP imaging, bands were processed using Image Lab Software (Bio-Rad Laboratories, Hercules, CA, USA). Western images were further analysed and quantified using ImageJ.

Loading controls were then checked and membranes were incubated in primary β-actin antibody (As described in Table Supplemental Table S8) in 1:1000 in 3% milk in TBST for 1 hour at room temperate and washed 3 X 10-15 minute in TBST. Secondary antibody incubation (As described in Supplemental Table S8) was then carried out in 1:5000 in 3% milk in TBST for 1 hour at room temperature and then washed 3 X 10-15 minute in TBST. Western blot signals were then developed and detected as mentioned above with ECL (Pierce, Thermo Scientific, Waltham, USA), and results were analysed using the same methods as above.

DNA Isolation and Dot Blots

DNA Isolation. DNA isolations were performed as published [7]. Briefly cells are trypsinised, collected and lysed in DNA lysis buffer (as described in Supplemental Table S9), and incubated at 55°C for 72 hours while shaking. Samples were centrifuged for 10 minutes at 13000 rpm and supernatant was removed. One volume of isopropanol was then added, and cells were incubated for 5 minutes at room temperature, centrifuged for 10 minutes at 12000 rpm at 4°C. Supernatant was removed and DNA pellet was washed and resuspended in 70% ethanol. Samples were centrifuged at 12000 rpm for 5 minutes at 4°C and supernatant was removed. Excess ethanol was left to evaporate, DNA pellet was resuspended in 50-100 μl nuclease free water. RNAse A digestion was then carried out with 200 μl/ml RNase A added/one million cells for 2 hours. Genomic DNA (gDNA) was then sonicated using BRANSON digital sonifier 450 (appliance number:364) for 20 cycles of 30 seconds on and off at 10% highest power. DNA was then quantified using Nano Drop 1000 and normalised.

Dot Blot. Dot blots were performed as published [7]. Briefly, one volume of DNA denaturing buffer was added to the normalised DNA sample and heated at 95°C for 10 minutes. Two volumes of 20X Saline-sodium citrate (SSC) (ENZ-GEN426-0250, Enzo, New York, USA) were then added and samples were left to cool on ice for 5 minutes. Serial dilution of DNA was prepared with DNA amount ranging from 5 μg to 0.2 μg and samples were pipetted on to Amersham Hybond-N+ blotting paper (GE Healthcare GERPN203B) and left partially dry. Membranes were wrapped using Saran Wrap and crosslinked using XL-1500 UV Crosslinker (Spectrolinker, appliance number 537, USA) at 1200J/m^2. Membrane was blocked in 5% milk in PBST for one hour, followed by overnight 5hmc primary antibody (As described in Supplemental Table S8) incubation at 4°C. On the following day, membrane was washed 3 x 10 minutes in TBST, followed by secondary antibody incubation (Describe in Supplemental Table S8)

and 3 x 10 minutes in TBST. Membrane was then developed and detected same as western blot using ECL (Millipore, Burlington, MA, USA). Results were then further analysed and quantified using ImageJ.

Clonogenic

Clonogenic assays were performed as previously described [8]. Briefly, cells were trypsinised, collected and counted as mentioned above. Cells were then seeded in different density ranging of 200 cell into 6-well plates and left to attach for four hours. Drugs are then added (as described in Supplemental Table S7) with 100 μM linagliptin/well and 100 μM Vitamin C and 20 μM metformin/well. Cells were incubated overnight. Within 24 hours of seeding, cells received sham radiation. Cells were further incubated for 24 hours, and media was refreshed with at least 3 ml complete media added into each well. Cells were incubated for 13 days. Colonies were then stained using 0.4% methylene blue and colonies with more than 50 cells were counted. Results were analysed using Prism 9.

Data and Image Analysis

Western blot and dot blot images captured using Chemidoc were processed using Image Lab Software (Bio-Rad Laboratories, Hercules, CA, USA) and further analysed using ImageJ. Results developed using x-ray films were scanned and quantified using ImageJ. All results obtained were analysed and compared using GraphPad Prism version 9. All experiments were performed at least three times and results were analysed using either unpaired two-way t-tests, one-way ANOVA, or two-way ANOVA. Data was presented as mean $\pm$ SD, and a threshold of $p<0.05$ was considered statically significant.

Supplemental Tables

Metrics	Models	A375	A549	HA1E	HCC515	HELA	HT29	MCF7	PC3	VCAP	YAPC
NDCG	TT-WOPT	0.7421 ± 0.0041	0.7367 ± 0.0103	0.7423 ± 0.0035	0.7346 ± 0.0059	0.7303 ± 0.0111	0.7468 ± 0.0091	0.7415 ± 0.0036	0.7298 ± 0.0028	0.7371 ± 0.0066	0.7386 ± 0.0044
	DeepCOP	0.8134 ± 0.0053	0.7980 ± 0.0091	0.7957 ± 0.0087	0.7960 ± 0.0031	0.8013 ± 0.0050	0.8253 ± 0.0073	0.8140 ± 0.0016	0.8123 ± 0.0044	0.8024 ± 0.0106	0.8152 ± 0.0086
	CIGER	**0.8357 ± 0.0067**	**0.8188 ± 0.0129**	**0.8254 ± 0.0047**	**0.8089 ± 0.0058**	**0.8332 ± 0.0169**	**0.8362 ± 0.0115**	**0.8276 ± 0.0101**	**0.8267 ± 0.0034**	**0.8298 ± 0.0073**	**0.8315 ± 0.0074**
P@10	TT-WOPT	0.2601 ± 0.0225	0.2476 ± 0.0179	0.2713 ± 0.0243	0.2482 ± 0.0129	0.2482 ± 0.0426	0.2790 ± 0.0419	0.2612 ± 0.0212	0.2499 ± 0.0258	0.2624 ± 0.0304	0.2813 ± 0.0556
	DeepCOP	0.5417 ± 0.0295	0.4935 ± 0.0502	0.5166 ± 0.0186	0.4975 ± 0.0187	0.5368 ± 0.0528	0.5865 ± 0.0201	0.5532 ± 0.0047	0.5757 ± 0.0323	0.5160 ± 0.0513	0.5913 ± 0.0447
	CIGER	**0.6021 ± 0.0363**	**0.5468 ± 0.0631**	**0.5840 ± 0.0139**	**0.5365 ± 0.0292**	**0.6432 ± 0.0530**	**0.6055 ± 0.0481**	**0.5898 ± 0.0330**	**0.6232 ± 0.0164**	**0.6248 ± 0.0231**	**0.6290 ± 0.0159**
P@50	TT-WOPT	0.2423 ± 0.0178	0.2345 ± 0.0160	0.2499 ± 0.0149	0.2328 ± 0.0096	0.2301 ± 0.0332	0.2552 ± 0.0283	0.2396 ± 0.0151	0.2290 ± 0.0211	0.2363 ± 0.0214	0.2427 ± 0.0354
	DeepCOP	0.4757 ± 0.0176	0.4373 ± 0.0428	0.4250 ± 0.0211	0.4267 ± 0.0136	0.4558 ± 0.0253	0.5122 ± 0.0179	0.4654 ± 0.0090	0.4951 ± 0.0246	0.4486 ± 0.0376	0.5072 ± 0.0301
	CIGER	**0.5420 ± 0.0302**	**0.4994 ± 0.0453**	**0.5134 ± 0.0055**	**0.4768 ± 0.0228**	**0.5578 ± 0.0509**	**0.5421 ± 0.0328**	**0.5191 ± 0.0355**	**0.5451 ± 0.0188**	**0.5435 ± 0.0188**	**0.5408 ± 0.0141**
P@100	TT-WOPT	0.2316 ± 0.0138	0.2249 ± 0.0194	0.2368 ± 0.0142	0.2229 ± 0.0039	0.2185 ± 0.0252	0.2369 ± 0.0235	0.2289 ± 0.0121	0.2193 ± 0.0137	0.2295 ± 0.0164	0.2321 ± 0.0290
	DeepCOP	0.4262 ± 0.0140	0.3902 ± 0.0345	0.3705 ± 0.0182	0.3856 ± 0.0072	0.4051 ± 0.0187	0.4613 ± 0.0185	0.4197 ± 0.0107	0.4418 ± 0.0193	0.4083 ± 0.0259	0.4395 ± 0.0215
	CIGER	**0.4877 ± 0.0239**	**0.4545 ± 0.0380**	**0.4632 ± 0.0052**	**0.4324 ± 0.0160**	**0.4984 ± 0.0490**	**0.4898 ± 0.0288**	**0.4672 ± 0.0321**	**0.4851 ± 0.0125**	**0.4757 ± 0.0131**	**0.4806 ± 0.0131**
P@200	TT-WOPT	0.2211 ± 0.0114	0.2167 ± 0.0154	0.2258 ± 0.0104	0.2122 ± 0.0048	0.2087 ± 0.0184	0.2224 ± 0.0172	0.2193 ± 0.0099	0.2108 ± 0.0109	0.2185 ± 0.0127	0.2219 ± 0.0225
	DeepCOP	0.3646 ± 0.0093	0.3389 ± 0.0228	0.3207 ± 0.0161	0.3339 ± 0.0068	0.3462 ± 0.0147	0.3931 ± 0.0129	0.3603 ± 0.0055	0.3722 ± 0.0119	0.3460 ± 0.0143	0.3687 ± 0.0150
	CIGER	**0.4172 ± 0.0180**	**0.3879 ± 0.0252**	**0.3991 ± 0.0031**	**0.3716 ± 0.0134**	**0.4163 ± 0.0385**	**0.4174 ± 0.0219**	**0.3973 ± 0.0240**	**0.4070 ± 0.0085**	**0.3998 ± 0.0081**	**0.4119 ± 0.0072**

Supplemental Table S1. Cell-specific performances (NDCG and Precision@K) of TT-WOPT, DeepCOP, and CIGER for up-regulated gene ranking under 5-fold cross-validation setting.

Metrics	Models	A375	A549	HA1E	HCC515	HELA	HT29	MCF7	PC3	VCAP	YAPC
NDCG	TT-WOPT	0.7625 ± 0.0033	0.7500 ± 0.0069	0.7583 ± 0.0043	0.7513 ± 0.0065	0.7500 ± 0.0084	0.7584 ± 0.0096	0.7477 ± 0.0038	0.7468 ± 0.0030	0.7508 ± 0.0083	0.7629 ± 0.0140
	DeepCOP	0.8441 ± 0.0032	0.8212 ± 0.0092	0.8258 ± 0.0051	0.8202 ± 0.0123	0.8173 ± 0.0039	0.8372 ± 0.0047	0.8245 ± 0.0058	0.8278 ± 0.0053	0.8394 ± 0.0073	0.8470 ± 0.0037
	CIGER	**0.8574 ± 0.0046**	**0.8378 ± 0.0096**	**0.8495 ± 0.0044**	**0.8251 ± 0.0087**	**0.8552 ± 0.0136**	**0.8519 ± 0.0053**	**0.8346 ± 0.0091**	**0.8412 ± 0.0015**	**0.8599 ± 0.0089**	**0.8625 ± 0.0028**
P@10	TT-WOPT	0.2916 ± 0.0093	0.2941 ± 0.0172	0.2984 ± 0.0072	0.2782 ± 0.0414	0.2657 ± 0.0499	0.3214 ± 0.0386	0.2806 ± 0.0160	0.2683 ± 0.0169	0.2893 ± 0.0298	0.2909 ± 0.0372
	DeepCOP	0.6355 ± 0.0167	0.5473 ± 0.0625	0.5334 ± 0.0288	0.5262 ± 0.0566	0.5316 ± 0.0612	0.6052 ± 0.0333	0.5883 ± 0.0198	0.5793 ± 0.0353	0.6178 ± 0.0379	0.6368 ± 0.0202
	CIGER	**0.6578 ± 0.0223**	**0.6151 ± 0.0611**	**0.6365 ± 0.0181**	**0.5472 ± 0.0329**	**0.6885 ± 0.0414**	**0.6522 ± 0.0258**	**0.6069 ± 0.0349**	**0.6198 ± 0.0201**	**0.6788 ± 0.0360**	**0.7004 ± 0.0520**
P@50	TT-WOPT	0.2708 ± 0.0032	0.2615 ± 0.0169	0.2653 ± 0.0117	0.2553 ± 0.0231	0.2480 ± 0.0362	0.2800 ± 0.0285	0.2611 ± 0.0111	0.2462 ± 0.0157	0.2674 ± 0.0305	0.2647 ± 0.0278
	DeepCOP	0.5473 ± 0.0163	0.4946 ± 0.0415	0.4748 ± 0.0230	0.4740 ± 0.0409	0.4652 ± 0.0234	0.5489 ± 0.0291	0.5157 ± 0.0160	0.5177 ± 0.0269	0.5479 ± 0.0317	0.5561 ± 0.0153
	CIGER	**0.5983 ± 0.0104**	**0.5523 ± 0.0436**	**0.5715 ± 0.0131**	**0.5038 ± 0.0267**	**0.6025 ± 0.0440**	**0.6019 ± 0.0220**	**0.5524 ± 0.0274**	**0.5655 ± 0.0074**	**0.6269 ± 0.0346**	**0.6162 ± 0.0132**
P@100	TT-WOPT	0.2562 ± 0.0034	0.2452 ± 0.0189	0.2494 ± 0.0092	0.2398 ± 0.0157	0.2309 ± 0.0285	0.2614 ± 0.0234	0.2481 ± 0.0133	0.2348 ± 0.0113	0.2503 ± 0.0251	0.2528 ± 0.0269
	DeepCOP	0.4890 ± 0.0127	0.4454 ± 0.0350	0.4348 ± 0.0219	0.4347 ± 0.0355	0.4213 ± 0.0164	0.4950 ± 0.0233	0.4648 ± 0.0125	0.4713 ± 0.0196	0.4925 ± 0.0269	0.5001 ± 0.0146
	CIGER	**0.5425 ± 0.0100**	**0.5078 ± 0.0344**	**0.5218 ± 0.0126**	**0.4652 ± 0.0243**	**0.5392 ± 0.0389**	**0.5530 ± 0.0226**	**0.5026 ± 0.0215**	**0.5183 ± 0.0045**	**0.5770 ± 0.0311**	**0.5543 ± 0.0114**
P@200	TT-WOPT	0.2358 ± 0.0068	0.2300 ± 0.0154	0.2324 ± 0.0084	0.2239 ± 0.0068	0.2189 ± 0.0225	0.2387 ± 0.0165	0.2304 ± 0.0110	0.2205 ± 0.0075	0.2318 ± 0.0188	0.2337 ± 0.0178
	DeepCOP	0.4144 ± 0.0080	0.3839 ± 0.0253	0.3855 ± 0.0155	0.3771 ± 0.0260	0.3706 ± 0.0101	0.4194 ± 0.0164	0.3985 ± 0.0101	0.4049 ± 0.0138	0.4214 ± 0.0170	0.4280 ± 0.0140
	CIGER	**0.4609 ± 0.0080**	**0.4273 ± 0.0267**	**0.4465 ± 0.0098**	**0.3985 ± 0.0169**	**0.4589 ± 0.0320**	**0.4680 ± 0.0161**	**0.4286 ± 0.0170**	**0.4422 ± 0.0046**	**0.4894 ± 0.0223**	**0.4657 ± 0.0084**

Supplemental Table S2. Cell-specific performances (NDCG and Precision@K) of TT-WOPT, DeepCOP, and CIGER for down-regulated gene ranking under 5-fold cross-validation setting.

Model	Classification Task			
	Up-regulated		Down-regulated	
	AU-PRC	F1	AU-PRC	F1
TT-WOPT	0.0527 ± 0.0010	0.0953 ± 0.0038	0.0563 ± 0.0013	0.0977 ± 0.0025
Logistic Regression	0.0848 ± 0.0065	0.1437 ± 0.0093	0.0961 ± 0.0053	0.1588 ± 0.0070
DeepCOP	0.1137 ± 0.0096	0.1733 ± 0.0078	0.1250 ± 0.0114	0.1894 ± 0.0126
CIGER	**0.1498 ± 0.0052**	**0.2226 ± 0.0076**	**0.1542 ± 0.0082**	**0.2335 ± 0.0083**

Supplemental Table S3. Performances (i.e., AU-PRC and F1) of TT-WOPT, Logistic Regression, DeepCOP, and CIGER for up-regulated and down-regulated gene classification under 5-fold cross-validation setting.

Up-regulated gene ranking					
Setting	NDCG	P@10	P@50	P@100	P@200
Full data	0.7761 ± 0.0029	0.4070 ± 0.0028	0.3447 ± 0.0042	0.3124 ± 0.0085	0.2804 ± 0.0091
Filtered data	**0.8275 ± 0.0041**	**0.5973 ± 0.0170**	**0.5276 ± 0.0126**	**0.4735 ± 0.0101**	**0.4027 ± 0.0077**
Down-regulated gene ranking					
Setting	NDCG	P@10	P@50	P@100	P@200
Full data	0.7966 ± 0.0049	0.4762 ± 0.0164	0.4079 ± 0.0173	0.3281 ± 0.0235	0.3182 ± 0.0136
Filtered data	**0.8460 ± 0.0023**	**0.6342 ± 0.0120**	**0.5753 ± 0.0041**	**0.5250 ± 0.0034**	**0.4465 ± 0.0035**

Supplemental Table S4. Average performances (NDCG and Precision@K) of CIGER when training with all gene expression profiles (i.e., full data) and high-quality gene expression profiles (i.e., filtered data) for ranking up-regulated and down-regulated genes under the 5-fold cross-validation setting.

	A375		A549		HA1E		HCC515		HELA		HT29		MCF7		PC3		VCAP		YAPC	
	Rank	P@200	Rank	P@200	Rank	P@200	Rank	P@200	Rank	P@200	Rank	P@200	Rank	P@200	Rank	P@200	Rank	P@200	Rank	P@200
Sucralfate	**4**	**0.3150**	**3**	**0.3300**	14	0.3200	**4**	**0.3400**	**3**	**0.3350**	**5**	**0.3700**	11	0.3300	**3**	**0.3250**	**8**	**0.3300**	**4**	**0.3400**
Inositol Hexasulphate	**6**	**0.3000**	**4**	**0.3200**	13	0.3200	**3**	**0.3500**	17	0.3250	**1**	**0.3900**	**3**	**0.3650**	**4**	**0.3200**	19	0.3100	**3**	**0.3450**
Ginsenoside B2	**7**	**0.3000**	**7**	**0.3100**	**2**	**0.3500**	**6**	**0.3300**	**4**	**0.3350**	**4**	**0.3750**	**7**	**0.3400**	**5**	**0.3150**	**9**	**0.3300**	**5**	**0.3350**
Madecassoside	**9**	**0.2850**	11	0.3000	**6**	**0.3300**	12	0.3250	**5**	**0.3350**	13	0.3500	14	0.3250	20	0.2800	15	0.3200	**6**	**0.3200**
Ginsenoside Rb1	13	0.2800	**10**	**0.3000**	**3**	**0.3400**	**9**	**0.3250**	12	0.3300	11	0.3550	15	0.3250	13	0.2900	11	0.3250	20	0.3100
Chromium gluconate	24	0.2400	15	0.2900	**5**	**0.3350**	**10**	**0.3250**	11	0.3300	16	0.3500	12	0.3250	15	0.2850	**10**	**0.3250**	15	0.3100
Sodium ferric gluconate complex	**5**	**0.3150**	**5**	**0.3100**	**9**	**0.3300**	13	0.3250	**9**	**0.3300**	28	0.3350	**9**	**0.3300**	**6**	**0.3050**	12	0.3200	26	0.3000
Betadex	**10**	**0.2800**	19	0.2850	19	0.3050	32	0.3000	**10**	**0.3300**	39	0.3250	13	0.3250	**8**	**0.3050**	**5**	**0.3350**	**10**	**0.3150**
Sucrosofate	**3**	**0.3200**	**2**	**0.3450**	11	0.3250	**1**	**0.3700**	**2**	**0.3500**	**2**	**0.3900**	**1**	**0.3700**	**2**	**0.3400**	**3**	**0.3450**	**2**	**0.3500**

Supplemental Table S5. Cell-specific ranks and the corresponding Precision@200 scores of pancreatic cancer's drug candidates calculated from our drug repurposing pipeline. Drugs in top 10 cell-specific evaluations are highlighted.

	A375		A549		HA1E		HCC515		HELA		HT29		MCF7		PC3		VCAP		YAPC	
	Rank	GSEA	Rank	GSEA	Rank	GSEA	Rank	GSEA	Rank	GSEA	Rank	GSEA	Rank	GSEA	Rank	GSEA	Rank	GSEA	Rank	GSEA
Dipyridamole	**2**	**0.3475**	3198	0.3021	**1**	**0.3565**	72	0.3388	119	0.2667	134	0.3270	23	0.2868	**1**	**0.3921**	**5**	**0.4107**	**1**	**0.3657**
Gedatolisib	886	0.0000	4464	0.0000	496	0.2597	59	0.3429	183	0.2480	**2**	**0.3626**	14	0.3006	**2**	**0.3640**	**8**	**0.4027**	**5**	**0.3449**
AZD-8055	886	0.0000	3732	0.2817	524	0.2565	**8**	**0.3770**	98	0.2716	1891	0.2684	**8**	**0.3108**	35	0.3098	11	0.4006	72	0.2935
Linagliptin	886	0.0000	10374	0.0000	620	0.2452	21	0.3626	206	0.2415	1050	0.2916	21	0.2946	**7**	**0.3272**	36	0.3756	**6**	**0.3386**
ZSTK-474	814	0.1893	4168	0.2498	435	0.2704	**7**	**0.3773**	181	0.2483	1006	0.2936	34	0.2774	37	0.3091	**2**	**0.4214**	**3**	**0.3524**
Biguanide	886	0.0000	**2**	**0.4528**	222	0.2882	2771	0.0000	687	0.1912	**3**	**0.3604**	946	0.0000	606	0.0000	200	0.3182	791	0.0000
CH-5132799	886	0.0000	3503	0.2914	880	0.2294	**6**	**0.3775**	81	0.2771	1511	0.2776	**10**	**0.3054**	117	0.2863	49	0.3715	73	0.2929
Vistusertib	886	0.0000	3627	0.2868	532	0.2555	**5**	**0.3778**	107	0.2701	1508	0.2776	**6**	**0.3185**	49	0.3049	**9**	**0.4012**	90	0.2889
Preladenant	886	0.0000	3988	0.2658	504	0.2589	94	0.3308	126	0.2650	656	0.3091	**7**	**0.3154**	**5**	**0.3342**	16	0.3935	**9**	**0.3338**

Supplemental Table S6. Cell-specific ranks and the corresponding GSEA scores of pancreatic cancer's drug candidates calculated from our drug repurposing pipeline. Drugs in top 10 cell-specific evaluations are highlighted.

Drug	Cat.No	Company	Stock concentration (mM)	Working concentration (uM)
AZD-8055	Lot 25910107	LKT lab	40	0.05
Preladenant (SCH-420814)	A3735	APExBIO	40	1
Linagliptin	A4034		100	100
Dipyridamole	B1933		100	100
Metformin	13118	Cayman Chemical	Prepare fresh	20
Vitamin C (L-sorbic Acid)	A92902-100G	Sigma-Aldrich		100

Supplemental Table S7. Drugs used for treatments with their stock concentration and working concentration.

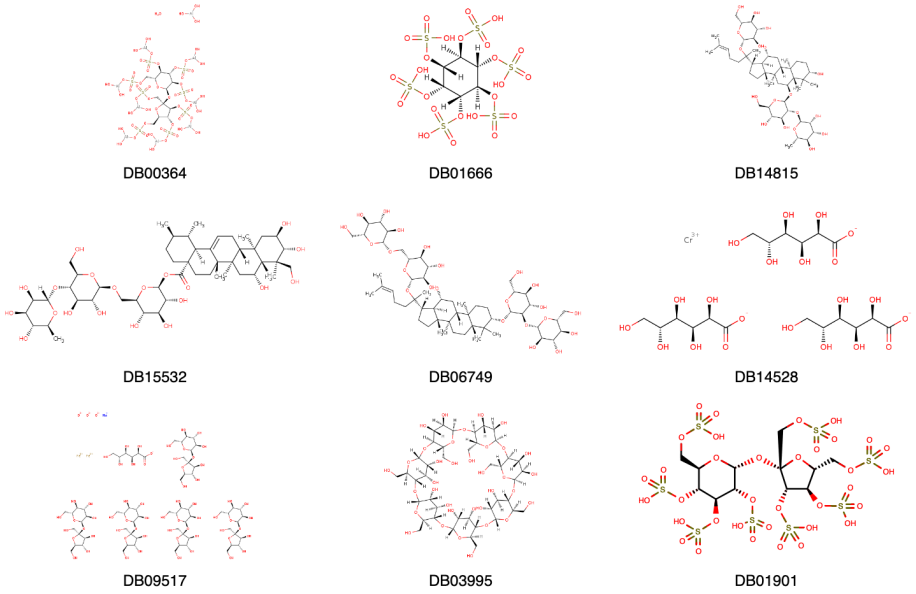
Antibody type	Company	Catalogue number	Dilution
TET2 primary	Abcam	ab124297	1:500
GATA6 primary antibody		ab22600	1:500
5hmc	Active Motif	39769	1:1000
b-actin	Proteintech	60008-1-1g	1:1000
Anti-Rabbit HRP	Cell Signal Technology	7074S	1:5000
Anti-Mouse HRP		7076S	1:5000
RNAse A	Thermo Scientific	EN0531	200 μg/ml/1x106 cells

Supplemental Table S8. Antibodies and enzyme used for western blot and blot bot with their working dilutions.

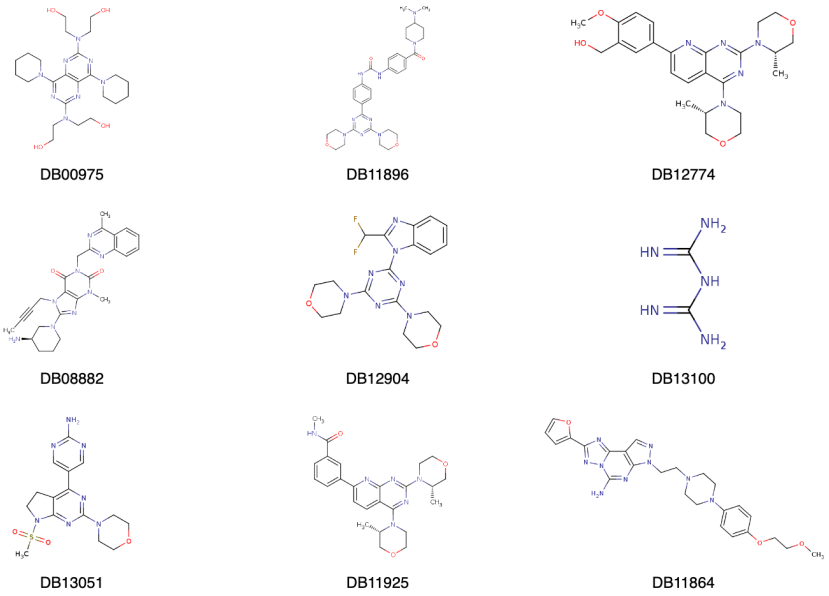
Buffer type	Content/company		Application
NuPAGE LDS Sample Buffer (4X)	NP0008	NuPAGE, Thermo Scientific, Waltham, USA	Western blot
NuPAGE MOPS SDS Running Buffer (20X)	NP0001-02		
Transfer buffer	Glycine 144 g, tris base 30.2 g		
Ripa Buffer	Thermo Fisher Ref 89900 Supplemented with protease inhibitor (Ref 04693116001, Roche, Basel, Switzerland) and phosphate inhibitor (Ref A32957 Pierce Thermo Scientific, Waltham, USA)		Western blot, protein extraction
Lysis Buffer	100 mM Tris-HCL [pH8.5], 5 mM EDTA, 0.2% SDS, 100mM NaCL, 0.5 mg/ml Proteinase K		Dot blot
Denaturing buffer	200 mM NaOH, 20mM EDTA		
TBS-0.1% Tween 20	6.05 Tris 8.76g NaCl, pH 7.6, with 0.1% Tween 20 (Acros Organics Cat 233360010)		Dot blot, Western blot

Supplemental Table S9. Buffers and solutions used in western blot and dot blot.

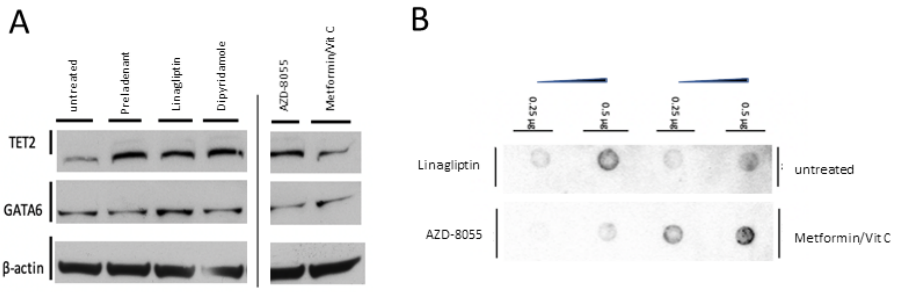
Supplemental Figures



Supplemental Figure S1. Molecular structures of drugs selected by our drug screening pipeline (w.r.t. Precision@200) as potential treatments for pancreatic cancer.



Supplemental Figure S2. Molecular structures of drugs selected by our drug screening pipeline (w.r.t. GSEA) as potential treatments for pancreatic cancer.



Supplemental Figure S3. Western blot and dot blot. (A) Western blot for TET2 and GATA6 level. (B) Dot blot for 5mhc.

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