SUPPLEMENTAL MATERIAL

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1 - Supplemental Methods

1.1 - Cell culture and reagents

HPTECs were purchased from Biopredic International (Rennes, France). Cells were cultured in collagen VI-coated flasks with DMEM/Ham's-F12 GlutaMAX medium (ThermoScientific) supplemented with 100 IU/mL penicillin/100 µg/mL streptomycin (Gibco), 36ng/mL hydrocortisone (HC, Sigma), 10 ng/mL epidermal growth factor (EGF, Promega), 1% insulin-transferrin-selenium (ITS, Lonza), and 4 pg/mL triiodothyronine (T3, Sigma) (Full medium). In screening experiments, HPTECs were kept in DMEM/Ham's-F12 GlutaMAX medium only supplemented with penicillin/ streptomycin (Free medium). Cells were maintained at 37°C in a humidified 5% CO_2 incubator and the medium was replaced one day after seeding and then every other day. For all experiments cells were used at passage 3.

Proliferation effect was compared to NIH 3T3 fibroblasts (ATCC, CRL-1658). Cells were cultivated in DMEM (ThermoScientific) supplemented with 10% bovine calf serum (BCS) and 100 IU/mL penicillin/100 µg/mL streptomycin (Gibco). In screening experiments BCS was reduced to 1%.

For the experiments with fibroblasts we followed the same experimental design used with HPTECs: cells were seeded in 96 well plates and kept in 1% bovine calf serum (BCS) for 48 hours. Induction of damage was performed using three different *in vitro* models of acute cell damage. 1) Hypoxia: (1% O_2); 2) 15µM, 10µM, 5µM and 2.5µM cadmium chloride ($CdCl_2$); 3) 5µM cyclosporine A (CycloA) or 75µM polymyxin (PMB) for 24h. The 15µM of $CdCl_2$ used to damage HPTECs induced complete cell death in fibroblasts and the experiments were carried out in three different concentrations (10µM, 5µM and 2.5µM) and we selected 5uM based on the amount of cell death of 20%,

measured by cell number after damage compared to undamaged cells. After 24h of damage, cells were treated with ID-8 or Harmine from 0.1nM to 1uM for 48h, or kept in 1% BCS medium. The proliferation effect was measured based on the percentage of EdU-labelled cells compared to the untreated control (1% BCS medium) in triplicates, from two biological replicates.

1.2 - EdU proliferation assay

To evaluate the percentage of actively proliferating cells four hours before fixing the cells, a modified thymidine analog, EdU (Click-iT EdU Plus, Invitrogen) was added to each well with a final concentration of 10uM. After the incubation period cells were taken out of the incubator and all procedures were carried out at room temperature: cells were fixed with 4% of paraformaldehyde for 20 minutes, permeabilized with 100% ice cold methanol for 10 minutes and washed 3 x with 3% BSA in 1x PBS. EdU incorporation and detection were performed according to manufacturer's instructions. Nuclei were stained with 0.1 µg/ml Hoechst 33342 for 30 minutes in the dark. Fluorescence imaging was performed using an Operetta High-Content Imaging System (PerkinElmer) at 10X magnification, long WD objective, 17 fields/ well.

1.3 - Damage protocol

To test the ability of compounds to induce proliferation after damage, primary HPTECs in passage 3 were seeded in collagen VI-coated 96 well plates (10,000 cells/well) and NIH/3T3 fibroblasts were seeded in 96 well plates (3,000 cells/well) using an automatic cell dispenser (WellMate, ThermoScientific). HPTECs were seeded in DMEM/Ham's-F12 GlutaMAX medium (ThermoScientific) supplemented with 100 IU/mL penicillin/100

µg/mL streptomycin (Gibco), 36 ng/mL hydrocortisone (HC, Sigma), 10 ng/mL epidermal growth factor (EGF, Promega), 1% insulin-transferrin-selenium (ITS, Lonza), and 4 pg/mL triiodothyronine (T3, Sigma) and fibroblasts in DMEM, 10% BCS and 100 IU/mL penicillin/100 µg/mL streptomycin (Gibco) (Full medium). On day 1 HPTEC full medium was replaced by new medium containing all the supplements described above, except for the EGF (EGF-free medium) and fibroblast full medium was replaced by DMEM, 10% BCS. Because this experiment resulted in cell loss and cell damage supplement-free medium was replaced by EGF-free medium in order to prevent excessive cell death. Cells were maintained in EGF-free medium or 1% BCS medium for 48 hours in order to abolish proliferation stimulus from the growth factor. On day 3 cells were either not damaged (control) or damaged with: 1) incubation at 1% O_2 (Hypoxia); or 2) 15µM of cadmium chloride ($CdCl_2$); or 3) 5µM of cyclosporine A (CycloA) or 75µM of polymyxin B (PMB) in EGF-free medium for 24h. On day 4, cells were maintained in EGF-free or 1% BCS medium (untreated and control groups) or treated with the following compounds:

1.4 - Secondary screen (selection of the eight hit compounds - only HPTECs): treatment with 10µM and 30µM of CGS21680; 1µM and 3µM of GDC-0152; 10µM and 30µM of SB505124; 3µM and 10µM of ZM336372; 1µM and 3µM of Fasudil; 10µM and 30µM of Iniparib; 3µM and 10µM of PD151746; or 10µM and 30µM of ID-8. Cells were treated for 24h, 72h and 96h.

1.5 - In vitro damage models and selection of final compound - only HPTECs: treatment with 0.1µM, 0.21µM, 0.46µM, 1µM, 2.1µM, 4.6µM, 10µM, 21µM, 46µM and 100µM of CGS21680; ZM336372; PD151746; or ID-8. Cells were treated for 96h.

1.6 - Experiment with different DYRK inhibitors after damage - only HPTECs: treatment with 1uM of Harmaline; Harmane; Norharmane; AZ191; Harmine; ID-8; INDY; TC-S 7004; and TG 003. Cells were treated for 48h.

1.7 - Dose-response experiments with ID-8 and Harmine - HPTECs and fibroblasts: treatment with 1µM, 0.1µM, 0.01µM, 0.001µM and 0.0001µM of ID-8 or Harmine. Cells were treated for 48h.

All compounds were dissolved in 100% DMSO in 10mM stock concentration and were added to the cells using D300 digital dispenser (Hewlett Packard). DMSO final concentration was normalized for all samples, except for control group which did not receive DMSO. Each experiment was performed using 3 biological replicates, in 3 technical replicates.

1.8 - Cell isolation, culture and seeding in 3 dimensional microphysiological system (3D MPS) platform

Healthy portions of the surgical specimen were dissected, stored at 4°C in Hanks balanced salt solution buffer containing penicillin-streptomycin, and processed for isolation of HPTECs within 24h. Confluent monolayer cultures of HPTECs with passage numbers 1 through 4 were suspended with 0.05% Trypsin-ethylenediamine tetraacetic acid, washed, counted, and resuspended at a concentration of 15 to 20 × 10^6 cells/mL. Approximately 5 µl of cell suspension were injected into the collagen IV–coated lumen of the 3D MPS platform (Nortis Inc.). Cells were allowed to adhere for 24 hours before

initiating media flow at 0.5 µl/min. Cell coverage and integrity of the tubule structure were assessed under light microscopy on a weekly basis.

1.9 - Library preparation and RNA sequencing

RNA samples were isolated using RNeasy plus (Qiagen) (n=3 /group) and were checked for quality (RIN value>8.0) and quantity using Agilent 2200 Bioanalyzer instrument and nanodrop (Thermo Scientific), respectively. RNA-seq libraries were prepared using Illumina TruSeq Stranded mRNA sample preparation kits (San Diego, CA) from 500ng of purified total RNA according to the manufacturer's protocol. The finished dsDNA libraries were quantified by Qubit fluorometer and the quality was assessed by Agilent Bioanalyzer 2200. Uniquely indexed libraries were pooled in equimolar ratios, which was quantitated by qPCR and then sequenced on two Illumina HiSeq High-Output run with single-end 75bp reads by the Biopolymers Facility at Harvard Medical School. All samples were processed using an RNA-seq pipeline implemented in the bcbio-nextgen project (https://bcbio-nextgen.readthedocs.org/en/latest/).[1] Raw reads were examined for quality issues using FastQC (http://www.bioinformatics.babraham.ac.uk/projects/fastqc/) to ensure library and sequencing suitability.

Reads were aligned to UCSC build mm10 of the Mus musculus genome, augmented with transcript information from Ensembl release 90 using STAR.[2] Alignments were checked for evenness of coverage, rRNA content, genomic context of alignments, complexity and other quality checks using a combination of FastQC, Qualimap,[3] MultiQC (https://github.com/ewels/MultiQC) and custom tools (Supplemental Figure 4A). Counts of reads aligning to known genes were generated by featureCounts.[4] Transcripts Per

Million (TPM) measurements per isoform were generated by quasi alignment using Salmon.[5] Data was loaded into R using bcbioRNASeq R package.[6] Covariate analysis, sample clustering and gene expression visualization were done with DEGreport R package.[7] Differential expression at the gene level was called with DESeq2,[8] using counts per gene estimated from the Salmon quasi alignments by tximport.[9] Lists of differentially expressed genes were examined for gene ontology (GO) and KEGG term enrichment with clusterProfiler.[10] In addition, a cut-off-free gene set enrichment analysis (GSEA) was performed using clusterProfiler and weighted fold change calculations from DESeq2.

1.10 Immunofluorescence

In order to validate upregulated genes found in the transcriptomics study at the protein level cells after treatment were fixed in 4% paraformaldehyde for 20' and permeabilized with 100% ice cold methanol for 10'. Cells were blocked with Odyssey buffer (Li-cor) for 1h at room temperature and incubated with conjugated antibodies and 0.1 µg/ml Hoechst 33342 overnight at 4°C. After incubation cells were washed 2x with 1x PBS-T and 2X with 1x PBS.

To stablish cell cycle phase we used a modified IF protocol previously described [11]. Briefly, four hours before fixing cells were pulsed with 10 µM of EdU (cycling cells, ThermoScientific) and with Live/Dead fixable far-red dead cell stain (LDR, 1:2000, ThermoScientific). After four hours of incubation cells were fixed, permeabilized and stained with anti-phospho-Histone H3 (chromosome condensation during mitosis) conjugated with Alexa 488 (Cell Signaling) and with 0.1 µg/ml of Hoechst 33342 (all nuclei) overnight at 4°C. After incubation cells were washed 2x with 1x PBS-T and 2X

with 1x PBS. Fluorescence imaging was performed using an Operetta High-Content Imaging System (PerkinElmer) at 10X magnification. Raw images were automatically analyzed for nuclei segmentation, intensity, roundness, border isolation and background (Columbus 2.4.2 Software, PerkinElmer). Twelve technical replicates were conducted on each biological replicate. Antibodies are listed in Supplemental Table 1.

1.11 - Western blot

Cells were harvested and lysed with M-PER Mammalian Protein Extraction Reagent (ThermoScientific) + 1X Halt protease and phosphatase inhibitor cocktail (ThermoScientific). Protein concentrations were determined using the BCA protein assay kit (Pierce, ThermoScientific), and equal amount of protein (20µg/sample, n=5-6/group) was loaded and run on a pre-casted 4-20% polyacrylamide gel (Bio-rad) and transferred to PVDF membranes (Bio-rad). Membranes were blocked with 5% milk in 1x TBS-T (Cell signaling) for 1h at room temperature and incubated with primary rabbit monoclonal anti-DYRK1A (Cell Signaling) overnight at 4^{o}.C followed by horseradish peroxidase (HRP) linked anti-rabbit secondary antibody (Cell Signaling). For protein normalization membranes were striped with Restore™ Western Blot Stripping Buffer (ThermoScientific) for 5’ and incubated with mouse monoclonal IgG anti-b-actin HRP linked (Santa Cruz) for 2h at room temperature. Bands were detected using enhanced chemiluminescence and captured with Synergy H1 Plate Reader (BioTek). Blots were quantified with the help of Image Studio Lite 5.2 software (Li-cor).

1.12 - References for Supplemental Methods

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2 - Supplemental Tables

Supplemental Table 1. List of antibodies used for immunocytochemistry, immunofluorescence and western blot

Protein	Primary	Dilution	Secondary	Dilution
Ki-67	ab15580, Abcam	1:100	ab150080, Alexa Fluor, 594 Abcam	1:1000
Epcam	ab20160, Abcam	1:100	ab150117, Alexa Fluor 488, Abcam	1:1000
PCNA	8580, Alexa Fluor 488 conjugated, Cell Signaling	1:500	-	-
E2F1	AB208078, Alexa Fluor 555 conjugated, Abcam	1:500	-	-
CCNB1	SC-752, Alexa Fluor 488 conjugated, Santa Cruz	1:500	-	-
CCNE2	50-9714-80, Alexa Fluor 647 conjugated, eBioscience	1:500	-	-
CCND1	MA1-39546, ThermoScientific	1:200	ab150117, Alexa Fluor 488, Abcam	1:1000
Phospho-Histone H3	3465S, Alexa Fluor 488 conjugated, Cell Signaling	1:1000	-	-
DYRK1A	2771, Cell Signaling	1:1000	7074 Anti-rabbit IgG, HRP linked, Cell Signaling	1:10000
B-actin	SC-47778, (C4) HRP linked, Santa Cruz	1:10000	-	-

Supplemental Table 2. List of the selected 129 hit compounds in the primary screen.

ID	Compound Name	Pathway	Targets	Replicate1	Replicate2	Average	Std Dev	CV
1	**SB505124**	TGF-beta/Smad	TGF-beta/Smad	1.45	1.36	1.407	0.06	4.5%
2	**GDC-0879**	MAPK	Raf	1.43	1.31	1.369	0.08	6.0%
3	**GDC-0152**	Apoptosis	IAP	1.39	1.28	1.336	0.08	6.2%
4	**BTZ043 Racemate**	Others	Others	1.24	1.39	1.315	0.11	8.4%
5	**N6022**	Others	Others	1.31	1.25	1.283	0.04	3.4%
6	**SSR128129E**	Angiogenesis	FGFR	1.26	1.29	1.274	0.02	1.4%
7	**Birinapant**	Apoptosis	IAP	1.31	1.23	1.269	0.06	4.6%
8	**TAK-438**	Transmembrane Transporters	Potassium Channel	1.33	1.20	1.264	0.09	7.4%
9	**Fasudil (HA-1077) HCl**	Cell Cycle	ROCK,Autophagy	1.30	1.20	1.252	0.07	5.3%
10	**Phenacetin**	Neuronal Signaling	COX	1.22	1.25	1.233	0.02	1.4%
11	**Pritelivir (BAY 57-1293)**	Others	Others	1.21	1.24	1.222	0.02	1.6%
12	**SC-514**	NF-κB	IκB/IKK	1.21	1.22	1.218	0.01	0.4%
13	**ZM 336372**	MAPK	Raf	1.22	1.20	1.209	0.01	1.0%
14	**Asaraldehyde**	Neuronal Signaling	COX	1.14	1.62	1.379	0.34	24.6%
15	**Tolbutamide**	Transmembrane Transporters	Potassium Channel	1.15	1.57	1.360	0.30	22.2%
16	**SB525334**	TGF-beta/Smad	TGF-beta/Smad	1.33	1.33	1.332	0.00	0.0%

ID	Compound Name	Pathway	Targets	Replicate1	Replicate2	Average	Std Dev	CV
17	**Rizatriptan Benzoate**	Neuronal Signaling	5-HT Receptor	1.18	1.45	1.317	0.19	14.6%
18	**Pancuronium dibromide**	Neuronal Signaling	AChR	1.53	1.07	1.299	0.32	24.7%
19	**Imatinib (STI571)**	Protein Tyrosine Kinase	PDGFR	1.15	1.36	1.254	0.14	11.5%
20	**Santacruzamate A (CAY10683)**	DNA Damage	HDAC	1.32	1.18	1.250	0.10	8.3%
21	**Ronidazole**	Others	Others	1.32	1.17	1.244	0.11	8.5%
22	**AGI-5198**	Metabolism	Dehydrogenase	1.29	1.19	1.239	0.07	5.5%
23	**Iniparib (BSI-201)**	DNA Damage	PARP	1.19	1.28	1.235	0.07	5.3%
24	**Scopine**	Neuronal Signaling	Adrenergic Receptor	1.06	1.40	1.230	0.25	20.0%
25	**Tigecycline**	Others	Others	1.23	1.23	1.229	0.00	0.0%
26	**INCB024360**	Metabolism	IDO	1.29	1.16	1.227	0.09	7.7%
27	**Glipizide**	Others	Others	1.11	1.34	1.226	0.16	13.0%
28	**Sulfanilamide**	Others	Others	1.18	1.27	1.223	0.07	5.4%
29	**Tariquidar**	Transmembrane Transporters	P-gp	1.31	1.13	1.222	0.13	10.2%
30	**Cefditoren Pivoxil**	Others	Others	1.14	1.30	1.222	0.11	9.4%
31	**Trelagliptin**	Proteases	DPP-4	1.24	1.19	1.218	0.04	3.0%
32	**Nevirapine**	Microbiology	Reverse Transcriptase	1.25	1.18	1.214	0.05	4.5%
33	**CRT0044876**	DNA Damage	APE	1.25	1.17	1.212	0.06	4.8%
34	**Naloxone HCl**	Neuronal Signaling	Opioid Receptor	1.11	1.31	1.208	0.14	11.6%
35	**FPH1 (BRD-6125)**	Others	Others	1.38	1.04	1.207	0.24	19.8%
36	**Valproic acid sodium salt**	Neuronal Signaling	Autophagy,HDAC ,GABA Receptor	0.99	1.41	1.202	0.29	24.4%
37	**Phenytoin sodium**	Transmembrane Transporters	Sodium Channel	1.19	1.22	1.202	0.02	1.7%
38	**Praziquantel**	Others	Others	1.31	1.09	1.200	0.15	12.7%
39	**Artemisinin**	Others	Others	1.24	1.15	1.197	0.07	5.4%
40	**Laquinimod**	Others	Others	1.31	1.08	1.192	0.16	13.7%
41	**E-64**	Proteases	Cathepsin K	1.20	1.18	1.191	0.02	1.4%
42	**Oxytetracycline (Terramycin)**	Others	Others	1.21	1.17	1.189	0.03	2.7%
43	**Chlorothiazide**	Others	Others	1.25	1.13	1.189	0.09	7.4%
44	**CORM-3**	Others	Others	1.14	1.23	1.189	0.06	5.3%
45	**Lincomycin HCl**	Others	Others	1.17	1.20	1.189	0.02	1.8%
46	**Phenoxybenzamine HCl**	GPCR & G Protein	Adrenergic Receptor	1.24	1.14	1.188	0.07	6.1%
47	**ID-8**	Others	Others	1.19	1.18	1.187	0.00	0.3%
48	**MM-102**	Epigenetics	Histone Methyltransferas e	1.10	1.27	1.185	0.12	9.7%
49	**Metolazone**	Others	Others	1.27	1.09	1.183	0.13	10.8%
50	**Pregnenolone**	Endocrinology & Hormones	Estrogen/progest ogen Receptor	1.18	1.18	1.182	0.00	0.2%
51	**Apocynin**	Others	Others	1.11	1.25	1.181	0.09	8.0%
52	**Tebipenem Pivoxil**	Others	Others	1.18	1.19	1.180	0.01	0.6%
53	**HA14-1**	Apoptosis	Bcl-2	1.20	1.16	1.180	0.02	1.8%
54	**Probucol**	Others	Others	1.23	1.13	1.179	0.07	6.1%
55	**Nalidixic acid**	Others	Others	1.22	1.14	1.178	0.05	4.5%
56	**Thiamet G**	Others	Others	1.21	1.15	1.178	0.04	3.6%
57	**Caspofungin Acetate**	Others	Others	1.25	1.11	1.178	0.10	8.4%
58	**Atglistatin**	Others	ATGL	1.18	1.17	1.176	0.01	1.0%

ID	Compound Name	Pathway	Targets	Replicate1	Replicate2	Average	Std Dev	CV
59	**Chloramphenicol**	Others	Others	1.20	1.16	1.176	0.03	2.4%
60	**（6-）ε-Aminocaproic acid**	Others	Others	1.14	1.21	1.175	0.05	3.9%
61	**Epinephrine Bitartrate**	GPCR & G Protein	Adrenergic Receptor	1.29	1.06	1.175	0.17	14.1%
62	**Fluocinolone Acetonide**	Others	Others	1.26	1.09	1.174	0.12	10.2%
63	**Etomidate**	Neuronal Signaling	GABA Receptor	1.08	1.27	1.172	0.13	11.2%
64	**PF-04620110**	Metabolism	Transferase	1.27	1.08	1.170	0.13	11.5%
65	**Moroxydine HCl**	Others	Others	1.17	1.16	1.170	0.01	0.6%
66	**Meprednisone**	Others	Others	1.15	1.19	1.170	0.03	2.4%
67	**Mirtazapine**	Others	Others	1.25	1.09	1.169	0.11	9.5%
68	**Sodium Nitroprusside**	Others	Others	1.18	1.16	1.169	0.02	1.6%
69	**NMDA (N-Methyl-D-aspartic acid)**	Neuronal Signaling	GluR	1.22	1.11	1.169	0.08	6.5%
70	**Nefiracetam**	Neuronal Signaling	GABA Receptor	1.18	1.15	1.168	0.02	1.7%
71	**CGS 21680 HCl**	Angiogenesis	5-alpha Reductase	1.28	1.05	1.168	0.16	14.1%
72	**EPZ5676**	Epigenetics	Histone Methyltransferas e	1.17	1.16	1.167	0.01	1.0%
73	**FPH2 (BRD-9424)**	Others	Others	1.28	1.05	1.166	0.16	13.7%
74	**Aminophylline**	Metabolism	PDE	1.10	1.23	1.164	0.09	8.0%
75	**Bosentan Hydrate**	GPCR & G Protein	Endothelin Receptor	1.16	1.17	1.162	0.01	0.8%
76	**D-Pantothenic acid**	Others	Others	1.07	1.25	1.162	0.13	11.2%
77	**Andarine**	Endocrinology & Hormones	Androgen Receptor	1.01	1.31	1.160	0.21	17.7%
78	**Methylprednisolone**	Others	Others	1.05	1.26	1.158	0.15	12.9%
79	**Articaine HCl**	Others	Others	1.14	1.18	1.157	0.03	2.2%
80	**Chlorpheniramine Maleate**	Neuronal Signaling	Histamine Receptor	1.00	1.31	1.157	0.22	18.9%
81	**Bepotastine Besilate**	Neuronal Signaling	Histamine Receptor	1.02	1.29	1.155	0.19	16.8%
82	**WY-14643 (Pirinixic Acid)**	Metabolism	PPAR	1.15	1.15	1.154	0.00	0.0%
83	**Penicillin G Sodium**	Others	Others	1.16	1.15	1.154	0.00	0.2%
84	**Limonin**	Others	Others	1.22	1.08	1.149	0.10	8.6%
85	**PD 151746**	Proteases	Cysteine Protease	1.16	1.14	1.149	0.02	1.3%
86	**IM-12**	PI3K/Akt/mTOR	GSK-3	1.21	1.09	1.149	0.08	7.0%
87	**Methoxsalen**	Others	Others	1.06	1.24	1.148	0.12	10.9%
88	**Valganciclovir HCl**	Others	Others	1.13	1.16	1.148	0.02	2.1%
89	**Naphazoline HCl**	Neuronal Signaling	Adrenergic Receptor	1.16	1.13	1.147	0.02	1.7%
90	**Acebutolol HCl**	Neuronal Signaling	Adrenergic Receptor	1.14	1.15	1.147	0.01	0.6%
91	**CK-636**	Cytoskeletal Signaling	Arp2/3	1.26	1.02	1.141	0.17	14.8%
92	**FH1(BRD-K4477)**	Others	Others	1.20	1.08	1.140	0.08	7.4%
93	**Eprosartan Mesylate**	Others	Others	1.22	1.06	1.139	0.12	10.3%
94	**Salicylanilide**	Others	Others	1.14	1.14	1.139	0.00	0.0%
95	**Isovaleramide**	Others	Others	1.20	1.08	1.138	0.09	7.6%
96	**Edoxaban**	Metabolism	Factor Xa	1.12	1.15	1.138	0.02	1.7%
97	**Glycyrrhizic Acid**	Others	Others	1.18	1.10	1.138	0.05	4.8%
98	**VGX-1027**	Others	Others	1.22	1.05	1.136	0.12	10.3%
99	**BV-6**	Apoptosis	IAP	1.21	1.07	1.136	0.10	8.7%

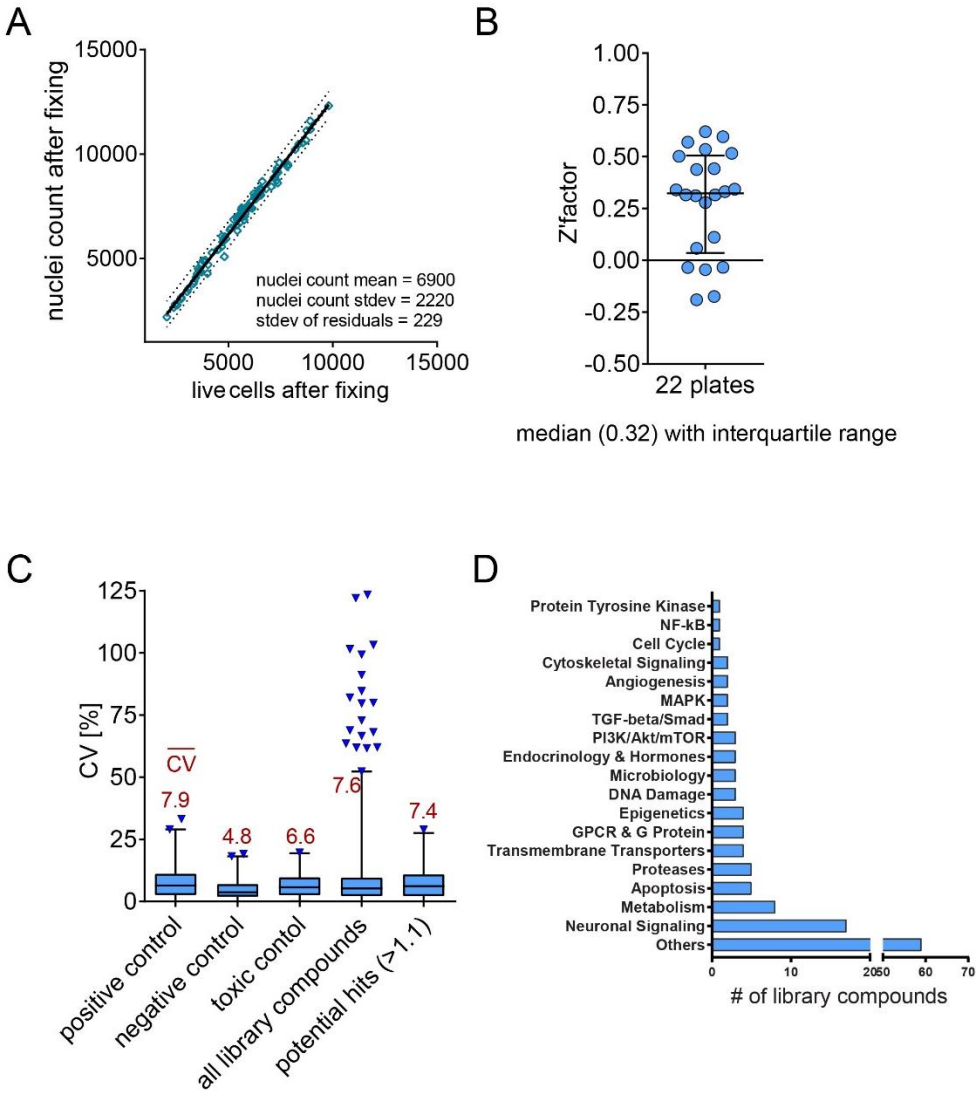
ID	Compound Name	Pathway	Targets	Replicate1	Replicate2	Average	Std Dev	CV
100	**Mitotane**	Others	Others	1.00	1.27	1.136	0.20	17.3%
101	**TIC10**	PI3K/Akt/mTOR	Akt	1.23	1.04	1.135	0.13	11.3%
102	**Mdivi-1**	Cytoskeletal Signaling	Dynamin	1.11	1.16	1.135	0.03	2.9%
103	**Semagacestat (LY450139)**	Proteases	Gamma- secretase	1.16	1.10	1.133	0.04	3.7%
104	**Levofloxacin**	Others	Others	1.14	1.11	1.129	0.02	1.9%
105	**AEBSF HCl**	Proteases	Serine Protease	1.24	1.02	1.129	0.16	14.1%
106	**Droperidol**	Others	Others	1.05	1.21	1.128	0.12	10.3%
107	**Exemestane**	Endocrinology & Hormones	Aromatase	1.14	1.12	1.128	0.02	1.5%
108	**Isotretinoin**	Metabolism	Hydroxylase	1.25	1.00	1.126	0.18	15.8%
109	**Ornidazole**	Others	Others	1.10	1.15	1.124	0.04	3.4%
110	**Betahistine 2HCl**	Neuronal Signaling	Histamine Receptor	1.23	1.02	1.123	0.14	12.8%
111	**Troxipide**	Others	Others	1.10	1.15	1.123	0.03	2.7%
112	**Pifithrin-α (PFTα)**	Apoptosis	p53,Autophagy	1.04	1.21	1.123	0.12	10.9%
113	**Inosine**	Others	Others	1.22	1.02	1.123	0.14	12.6%
114	**C646**	Epigenetics	Histone Acetyltransferase	1.13	1.12	1.123	0.01	0.9%
115	**Dimethyl Fumarate**	Others	Others	1.10	1.15	1.122	0.03	2.9%
116	**Apixaban**	Metabolism	Factor Xa	1.14	1.10	1.122	0.03	2.4%
117	**Amprolium HCl**	Others	Others	1.13	1.11	1.120	0.02	1.7%
118	**Erdosteine**	Others	Others	1.12	1.12	1.118	0.00	0.3%
119	**EPZ004777**	Epigenetics	Histone Methyltransferas e	1.04	1.20	1.117	0.11	10.1%
120	**Prednisone**	Others	Others	1.12	1.11	1.115	0.01	0.8%
121	**Chloroprocaine HCl**	Others	Others	1.10	1.13	1.115	0.02	1.7%
122	**Empagliflozin (BI 10773)**	GPCR & G Protein	SGLT	1.12	1.10	1.113	0.01	1.3%
123	**Lafutidine**	Neuronal Signaling	Histamine Receptor	1.13	1.10	1.112	0.02	2.1%
124	**Dibenzothiophene**	Others	Others	1.12	1.10	1.111	0.02	1.5%
125	**Etravirine (TMC125)**	Microbiology	Reverse Transcriptase	1.02	1.21	1.110	0.13	12.1%
126	**Risperidone**	Neuronal Signaling	5-HT Receptor	1.22	1.00	1.109	0.16	14.5%
127	**Emtricitabine**	Microbiology	Reverse Transcriptase	1.20	1.02	1.107	0.13	11.7%
128	**SB216763**	PI3K/Akt/mTOR	GSK-3	1.11	1.10	1.104	0.01	0.8%
129	**Vitamin B12**	Others	Others	1.11	1.10	1.103	0.01	0.6%

Supplemental Table 3. Fold change and *p* values of cell cycle proteins modulated by the treatment with ID-8 or Harmine after different types of damage

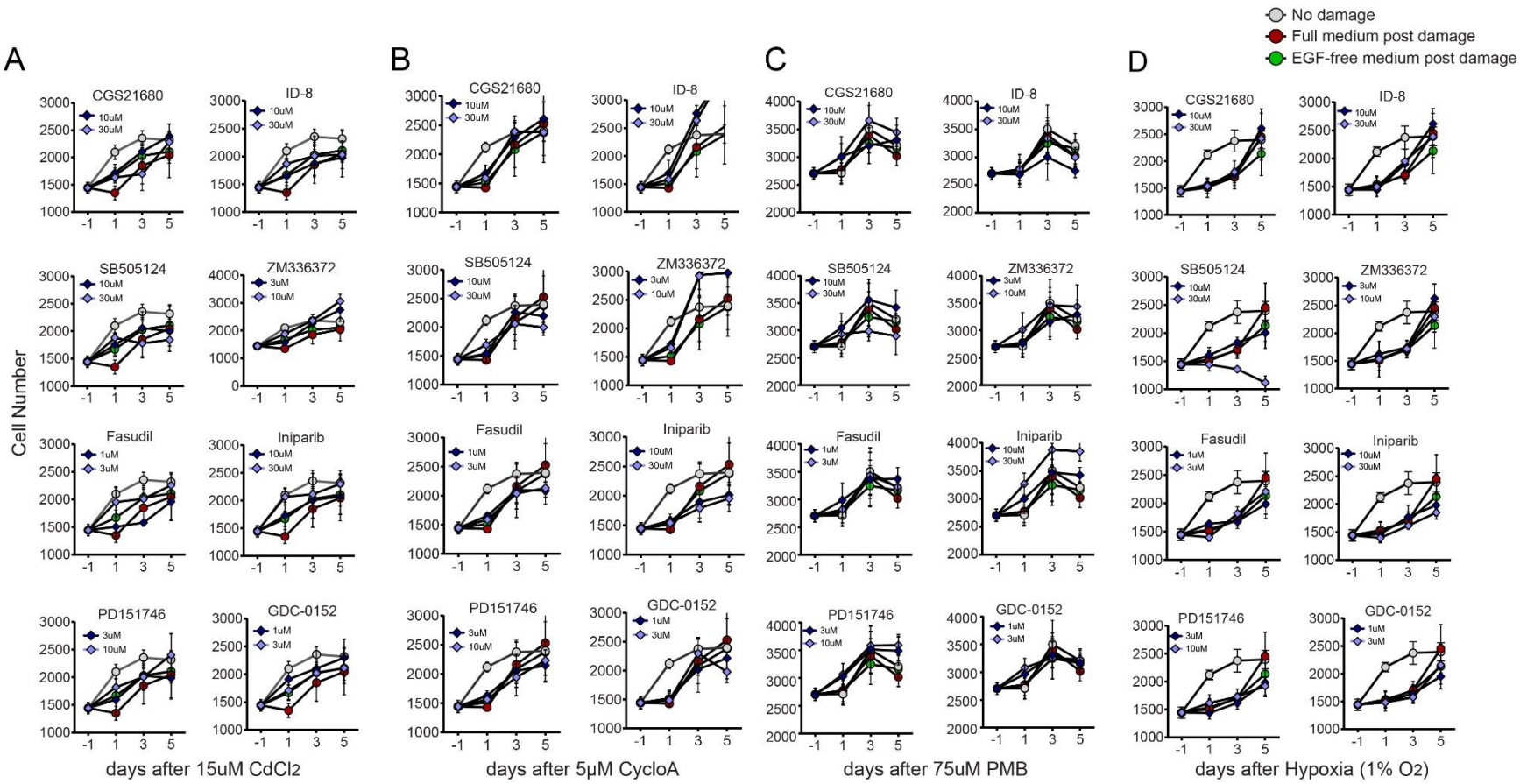
	ID-8 (1µM)				Harmine (1µM)			
	$CdCl_2$ (15µM)	**CycloA (5µM)**	**PMB (75µM)**	**Hypoxia**	**$CdCl_2$ (15µM)**	**CycloA (5µM)**	**PMB (75µM)**	**Hypoxia**
PCNA*	1.3/ 0.0001	1.4/ 0.0001	1.1/ 0.0001	1.1/ 0.0001	1.16/ 0.0001	1.3/ 0.0001	1.1/ 0.0001	1.1/ 0.03
E2F1*	1.2/ 0.0001	1.3/ 0.0001	1.1/ 0.0001	1.2/ 0.0003	NS	1.2/ 0.0001	1.1/ 0.0001	NS
CCNB1*	NS	1.2/ 0.01	1.1/ 0.02	1.3/ 0.01	NS	NS	NS	NS
CCNE2*	1.4/ 0.004	1.5/ 0.005	NS	NS	1.3/ 0.02	NS	NS	NS

*Fold Change to untreated group (EGF-free medium)/adjusted *p* values

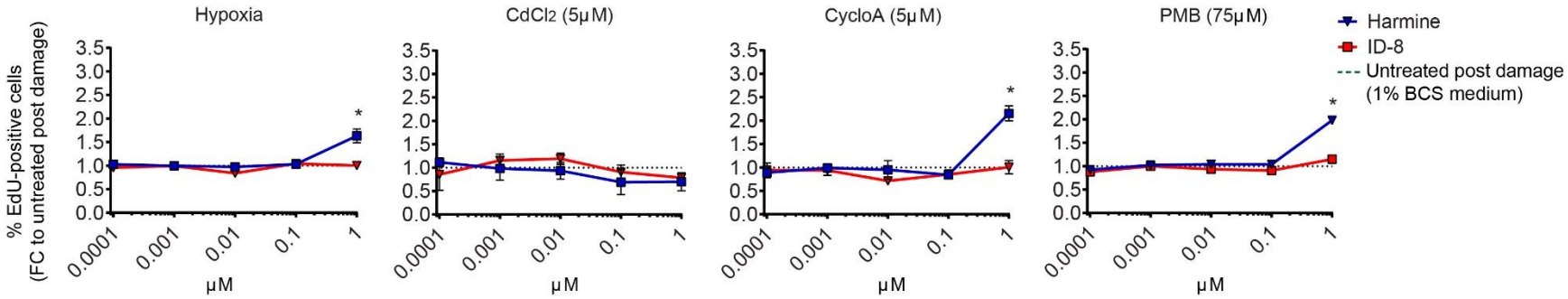
3 - Supplemental Figures



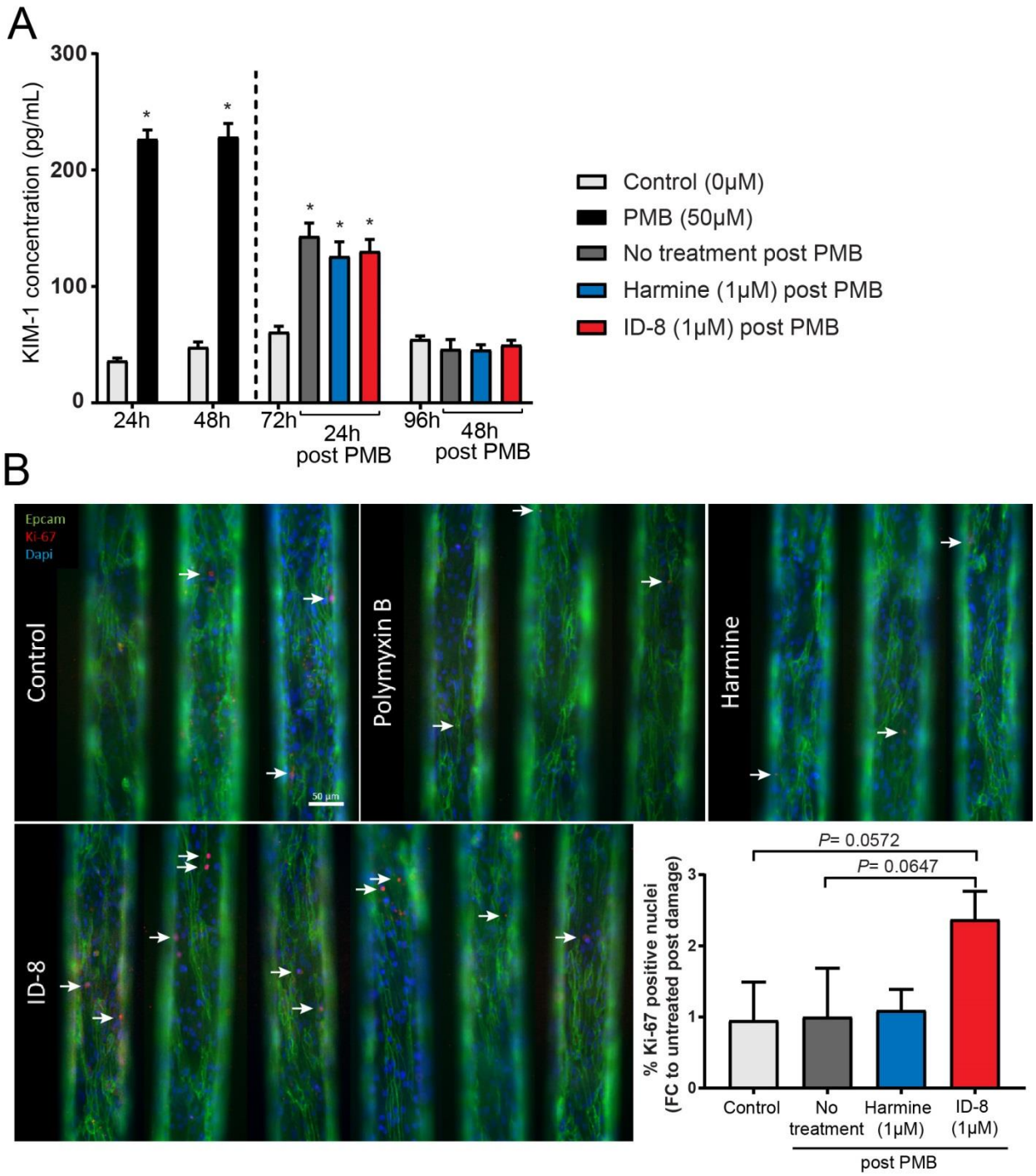
Supplemental Figure 1. Primary screen shows compounds with potential pro-proliferative effects in primary human proximal tubular epithelial cells (HPTECs). A-C) Primary screen quality control. D) Main pathways activated by the hit compounds.



Supplemental Figure 2. Compounds CGS21680, ZM336372, PD151746 and ID-8 promoted proliferation of primary human proximal tubular epithelial cells (HPTECs) in, at least, two types of damage. Selection of the compounds promoting cell proliferation after damage with A) 15µM of $CdCl_2$; B) 5µM of cyclosporine A; C) hypoxia (1% O_2) and 75µM of polymyxin B. Data are represented as mean ± SEM of the total cell number. n=3/group, 3 biological replicates

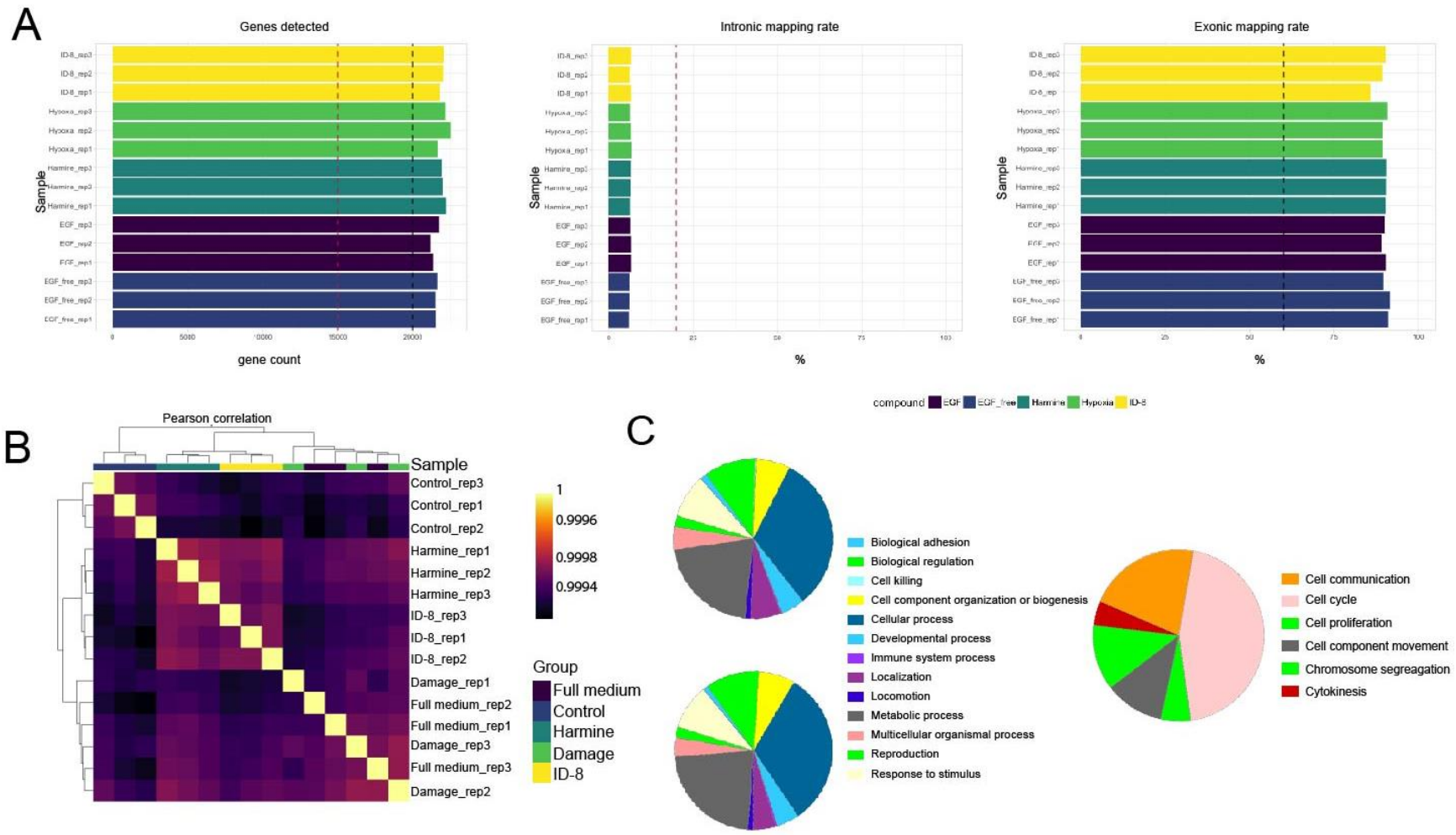


Supplemental Figure 3. DYRK1A inhibitor ID-8 does not promote proliferation of NIH/3T3 fibroblasts after damage. Dose response curve after 48h of treatment with ID-8 and Harmine in NIH/3T3 fibroblasts after 24h of damage with hypoxia (1% O_2), 5µM of $CdCl_2$, 5uM of cyclosporine A (CycloA), or 75µM of polymyxin B (PMB) (n= 3/group, 2 biological replicates). EdU-positive cells were normalized to the total cell number per well. Data are presented as mean ± SEM of the fold change over the untreated group (1% bovine calf serum medium, BCS). *P<0.05 after correction for multiple comparisons.



Supplemental Figure 4. ID-8 promotes proliferation of primary human proximal tubular epithelial cells (HPTECs) in 3 dimensional microphysiological system (3D MPS). (A) KIM-1 expression in effluents from devices: without damage (control) for 24h, 48h, 72h and 96h and damaged with 50µM of polymyxin B (PMB) for 24h and 48h

followed by 24h and 48h of polymyxin B washout (no treatment) or treatment with 1µM of Harmine or ID-8; (B) Ki-67 (white arrows) and epcam staining (green) in 3D MPS maintained in EGF-free medium (control) or damaged with 50µM of polymyxin B (PMB) followed by 48h treatment with 1µM of Harmine or ID-8 or no treatment (EGF-free medium) (*P< 0.05 after multiple comparisons). n=3-6 biological replicates/group



Supplemental Figure 5. RNA sequencing identifies differentially expressed genes after ID-8 and Harmine treatment post-damage. A) RNAseq analysis quality control showing the number of detected genes, low intronic and

high exonic mapping rates for the tested samples. B) Sample-sample correlation heat map showing intra-group variation. C) Panther classification system of the most upregulated genes after treatment with 1uM of ID-8 or Harmine