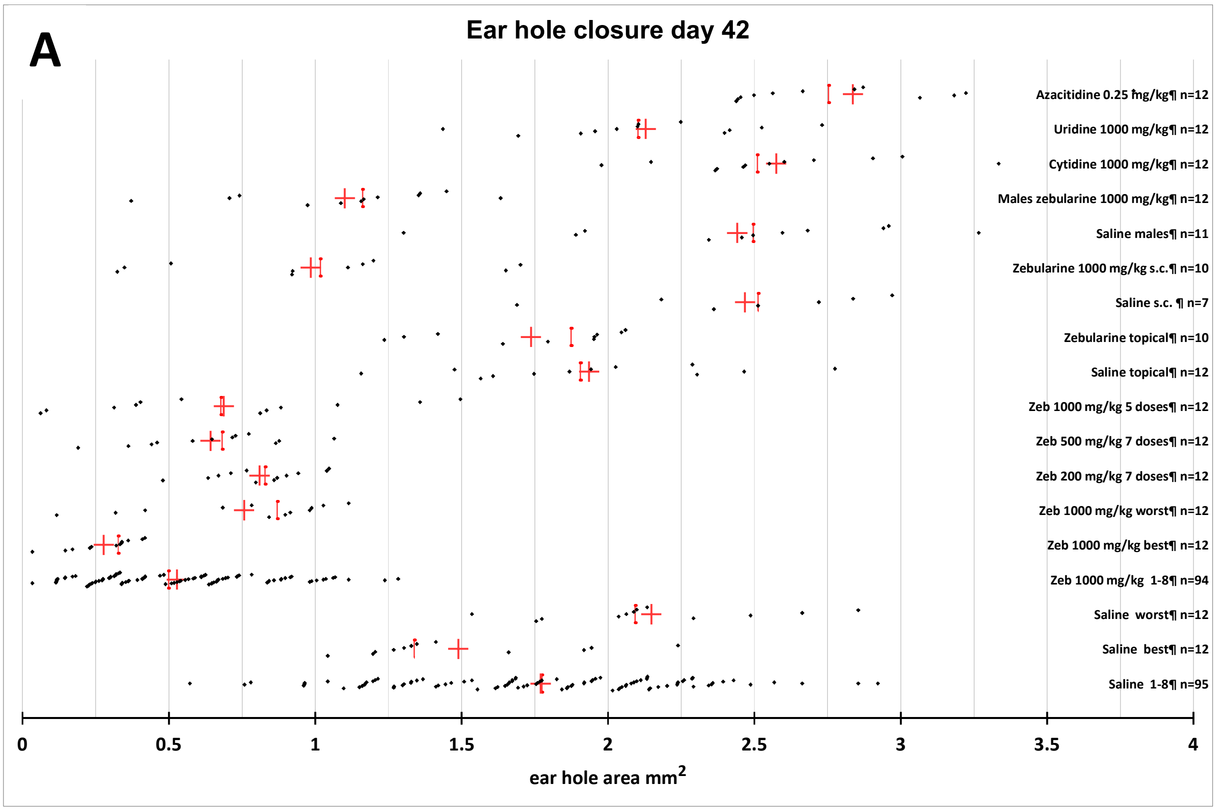

B. Pairwise comparisons performed using the Mann-Whitney test

p-value	vs. Saline best healing group	vs. Saline worst healing group	vs. Zeb best healing group	vs. Zeb worst healing group
Azacitidine 0.25 mg/kg¶ n=12	**7.40E-07**	**1.11E-03**	**7.40E-07**	**7.40E-07**
Uridine 1000 mg/kg¶ n=12	**9.01E-04**	9.77E-01	**7.40E-07**	**7.40E-07**
Cytidine 1000 mg/kg¶ n=12	**6.01E-05**	**1.66E-02**	**7.40E-07**	**7.40E-07**
Males zebularine 1000 mg/kg¶ n=12	**4.04E-02**	**4.69E-05**	**6.01E-05**	**1.94E-02**
Saline males¶ n=11	**1.23E-03**	1.32E-01	**1.48E-06**	**1.48E-06**
Zebularine 1000 mg/kg s.c.¶ n=10	**1.11E-02**	**1.50E-04**	**8.69E-04**	1.56E-01
Saline s.c. ¶ n=7	**1.53E-03**	9.93E-02	**3.97E-05**	**3.97E-05**
Zebularine topical¶ n=10	8.06E-02	**1.11E-02**	**3.09E-06**	**3.09E-06**
Saline topical¶ n=12	**2.26E-02**	1.94E-01	**7.40E-07**	**7.40E-07**
Zeb 1000 mg/kg 5 doses¶ n=12	**1.35E-03**	**7.40E-07**	**2.62E-02**	4.70E-01
Zeb 500 mg/kg 7 doses¶ n=12	**4.69E-05**	**7.40E-07**	**4.78E-04**	2.14E-01
Zeb 200 mg/kg 7 doses¶ n=12	**4.69E-05**	**7.40E-07**	**7.40E-07**	9.77E-01
Zeb 1000 mg/kg worst¶ n=12	**4.69E-05**	**7.40E-07**	**2.01E-03**	1.00E+00
Zeb 1000 mg/kg best¶ n=12	**7.40E-07**	**7.40E-07**	1.00E+00	**2.01E-03**
Zeb 1000 mg/kg 1-8¶ n=94	**3.41E-08**	**1.92E-08**	**7.42E-03**	**1.42E-02**
Saline worst¶ n=12	**1.11E-03**	1.00E+00	**7.40E-07**	**7.40E-07**
Saline best¶ n=12	1.00E+00	**1.11E-03**	**7.40E-07**	**4.69E-05**
Saline 1-8¶ n=95	**4.35E-02**	**1.49E-02**	**1.88E-08**	**1.63E-07**

Fig. S1. Ear hole closure data. Ear hole areas at d42 presented as dot plots **(A)** and complimentary pairwise comparisons with the best and worst healing groups **(B)**.

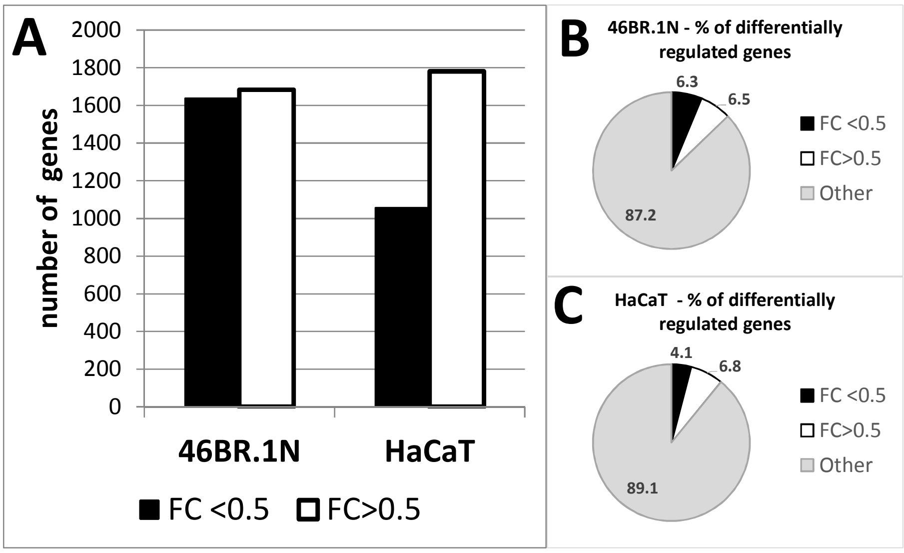

Fig. S2. Transcriptional response to zebularine stimulation in cultured human fibroblasts (46BR.1N) and keratinocytes (HaCaT) determined using RNAseq. (A) Numbers of genes showing a minimum two fold-change (FC); **(B)** Percentage of up- and downregulated genes in the fibroblasts (46BR.1N) and **(C)** keratinocytes (HaCaT).

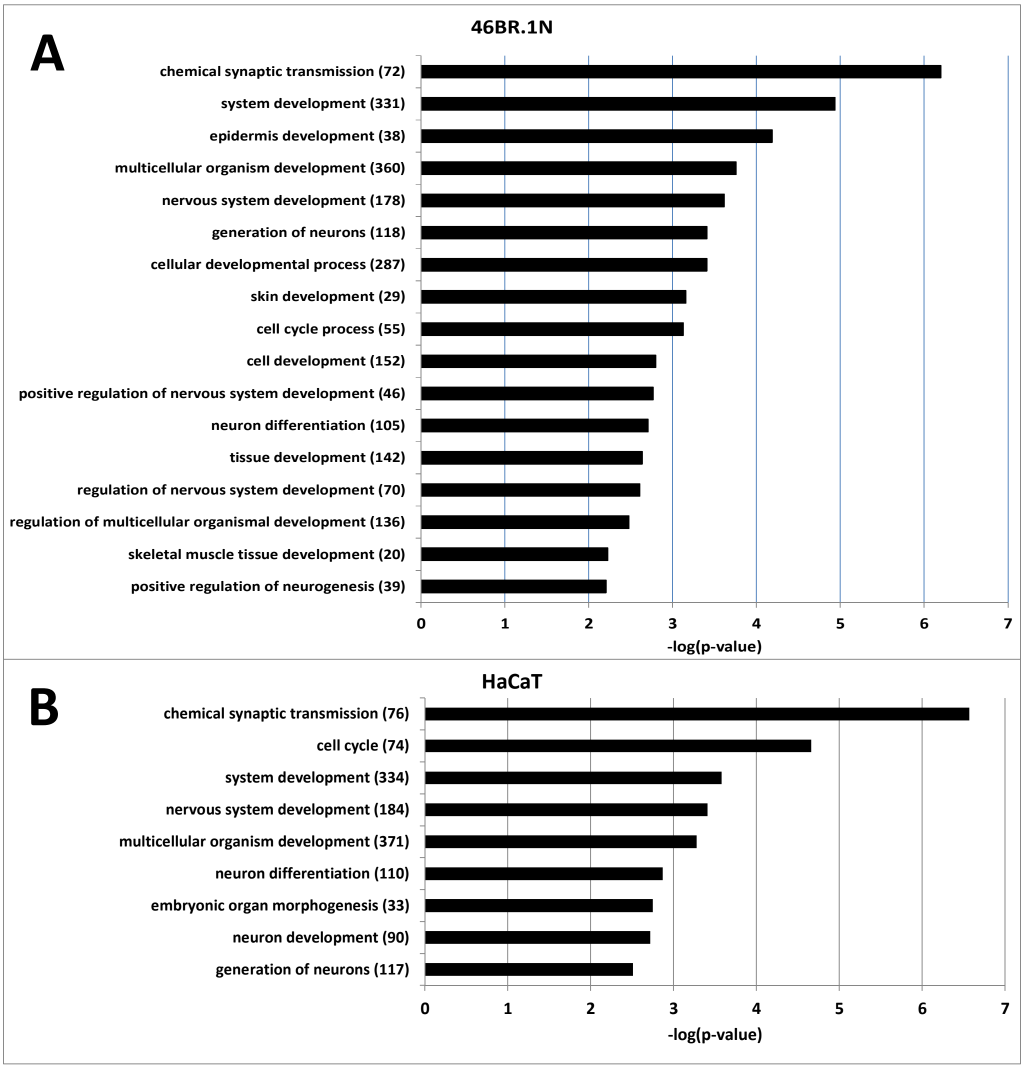

Fig. S3. Gene ontology analyses for the genes upregulated (FC>2.0) under zebularine stimulation in cultured human (A) fibroblasts (46BR.1N) and (B) keratinocytes (HaCaT). Statistical significance is presented as -log10 of p-value.; the numbers of upregulated genes belonging to enriched functional categories are given in parentheses.

Gene ontology analysis conducted for the upregulated transcripts (fold change >2.0) exposed a significant enrichment of a number of functional categories. Of note is the enrichment of developmental genes, in particular of those involved in neuronal development in both cell lines (**Fig. S2a, b**). This finding corresponds to the transcriptional responses in the ear pinna in zebularine-treated mice, in which we observed a remarkable upregulation of several neurodevelopmental genes **(Fig. 5)**. Also of note is an enrichment of cell-cycle and synaptic transmission genes.

Table S1. PCR primer sequences.

Gene	**Assay**	**Organism**	**Primer forward**	**Primer reverse**	**Location**
Actb	gene expression	*M. musculus*	GGCTGTATTCCCCTCCATCG	CCAGTTGGTAACAATGCCATGT	
Bdnf	gene expression	*M. musculus*	ATTAGCGAGTGGGTCACAGC	ATTGCGAGTTCCAGTGCCTT	
Dnmt1	gene expression	*M. musculus*	TCCCCTACAATGGAGAGCCA	CACCTGTATGTTGGGCAGGT	
Dnmt3a	gene expression	*M. musculus*	TAGCGGGTGCTTACTTGTGG	GGAACCGAAAGAGGACCAGG	
Dnmt3b	gene expression	*M. musculus*	CCACATTTGCTGGAGGATGC	CTGCCAGGGAAAAGCCCTAA	
Dnmt3l	gene expression	*M. musculus*	GTTTGCTTTCAGGCCTTCGG	AGGTTATCCCACCGGGAACT	
Myc	gene expression	*M. musculus*	CTTTCCCTACCCGCTCAAC	GCCTCTTCTCCACAGACACC	
Myt1l	gene expression	*M. musculus*	CGGAACCCAGACATGGAGGT	CTACAGGCAAGTCCCAGCAA	
Nanog	gene expression	*M. musculus*	TACCTCAGCCTCCAGCAGAT	CCAGATGCGTTCACCAGATA	
Neurod1	gene expression	*M. musculus*	GCTACTCCAAGACCCAGAAAC	TGTACGAAGGAGACCAGATCA	
Neurod6	gene expression	*M. musculus*	TTACAGCTCAACGCCAGAAG	TGTGGTAGGGTGGGTAGAAT	
Ngf	gene expression	*M. musculus*	GCTCACCTCAGTGTCTGGGC	AGGGCTGTGTCAAGGGAATGCT	
Nog	gene expression	*M. musculus*	CCAGCACTATCTACACATC	TCTCGTTCAGATCCTTCTCCT	
Ntf3	gene expression	*M. musculus*	CAAGCTGATCCAGGCGGATA	GCGTCTCTGTTGCCGTAGTA	
Pou5f1	gene expression	*M. musculus*	GGAGAAGTGGGTGGAGGAAG	TGATTGGCGATGTGAGTGAT	
Sox1	gene expression	*M. musculus*	CTTCATGGTGTGGTCCCG	TTGCTGATCTCCGAGTTGTG	
Sox2	gene expression	*M. musculus*	GGGAGAAAGAAGAGGAGAGAGA	CGATTGTTGTGATTAGTTTTTGGA	
Tdg	gene expression	*M. musculus*	GGCATTTTATGCGGGTGCTT	TCCAGTGGGGAGGAATACCAT	
Tbp	gene expression	*M. musculus*	GAGAGCCACGGACAACTGCG	GGGAACTTCACATCACAGCTC	
Tet1	gene expression	*M. musculus*	GGGCAGCTTTTGCATTGTGA	ATGCCTTATTCCCACCACCG	
Tet2	gene expression	*M. musculus*	TGCGTCAGTGGAGACCTTTG	CACTGCCTTCCTCCCTACAC	
Tet3	gene expression	*M. musculus*	GGAGCCATAGGCTTCTCACC	TGAATGACGAGCAGTCGGAG	
ACTB	gene expression	*H. sapiens*	CATGGGTCAGAAGGATTCCT	ACACGCAGCTCATTGTAGAA	
GABPRP	gene expression	*H. sapiens*	CAGCCAACAGTACCAAAAGTGATT	TGGCGAGATTGTCTAAAATAACTGA	
GAPDH	gene expression	*H. sapiens*	TGCACCACCAACTGCTTAG	GATGCAGGGATGATGTTC	
KRT7	gene expression	*H. sapiens*	GCGTGAGTACCAGGAACTCATG	GCTTGCGGTAGGTGGCG	
MEIS1	gene expression	*H. sapiens*	GCCTATCGATTTGGTGATAG	ACTGGTCTATCATGGGCTGC	
NKX2-5	gene expression	*H. sapiens*	TTCCCGCCGCCCCCGCCTTCTAT	CGCTCCGCGTTGTCCGCCTCTGT	
POU6F2	gene expression	*H. sapiens*	ATGTCTCAAAGTCCCGTCCG	GCCGTTTGAGGATTGCTGAC	
PPARG	gene expression	*H. sapiens*	GAGAAGGAGAAGCTGTTGGC	ATGGCCACCTCTTTGCTCT	
TBP	gene expression	*H. sapiens*	TGCACAGGAGCCAAGAGTGAA	CACATCACAGCTCCCCACCA	
Bdnf	DNA methylation	*M. musculus*	GCAAGTCCTGTGTGGCCTTTTGGTTCC	AAGCAGTCTGAGCAGGAGCAGTATGA	-29:-160 from TSS
Nanog	DNA methylation	*M. musculus*	GGCTGGGCAATGGAGGCAGTAGT	CCAAGCCACCATTGTTACCACTGCC	-1910: -1609 from TSS
Nanog	DNA methylation	*M. musculus*	ACTCACTTATCTGTGAGCACAAGG	CTTCAGACTTACTGCAATCCCAAGT	-982: -755 from TSS
Nanog	DNA methylation	*M. musculus*	CCAAAGCATGGACCAACTTA	GACCTTGCTGCCAAAGTCTC	-597: -406 from TSS

Table S2. Power statistics

Figure	Time Point	Sample 1	Sample 2	Sample size 1	Sample size 2	α (alpha)	Mean 1	Mean 2	SD 1	SD 2	Beta	Power
Fig. 1f	d42	Saline	Zebularine i.p. 1000 mg/kg	95	94	0.05	0.437	0.832	0.154	0.094	< 0.0001	1.000
Fig. 2a	d42	Saline	Zebularine i.p. 200 mg/kg	95	12	0.05	0.437	0.742	0.154	0.054	< 0.0001	1.000
Fig 2a	d42	Saline	Zebularine i.p. 500 mg/kg	95	12	0.05	0.437	0.796	0.154	0.075	< 0.0001	1.000
Fig. 2a	d42	Saline	Zebularine i.p. 1000 mg/kg 5 doses	95	12	0.05	0.437	0.781	0.154	0.149	< 0.0001	1.000
Fig. 2b	d42	Saline s.c.	Zebularine s.c. 1000 mg/kg	7	10	0.05	0.214	0.447	0.140	0.101	0.070	0.930
Fig. 2c	d42	Saline males	Zebularine i.p. 1000 mg/kg males	11	12	0.05	0.223	0.650	0.179	0.113	< 0.0001	1.000
Fig. 2d	d42	Saline C57BL/6J	Zebularine i.p. C57BL/6J	32	24	0.05	0.011	0.611	0.238	0.193	< 0.0001	1.000
Fig. 2e	d42	Saline	Uridine 1000 mg/kg	95	12	0.05	0.437	0.322	0.154	0.117	0.375	0.625
Fig. 2e	d42	Saline	Cytidine 1000 mg/kg	95	12	0.05	0.437	0.180	0.154	0.119	0.001	0.999
Fig. 2e	d42	Saline	5-azacytidine 0.25mg/kg	95	12	0.05	0.437	0.097	0.154	0.133	0.027	0.973
Fig. 4a	d7	CpG metylation saline	CpG methylation Zebularine	8	8	0.05	29.08	20.45	4.73	2.49	< 0.0001	1.000
Fig. 6b	d21	Control	Zebularine+ RA	24	35	0.05	0.403	0.978	0.145	0.022	< 0.0001	1.000