

## SUPPLEMENTARY FILES

### **Grainyhead 1 acts as a drug-inducible conserved transcriptional regulator linked to insulin signaling and lifespan**

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File Name: Supplementary Data 1

File Type: Excel Workbook (\*.xlsx)

Description: *C. elegans* lifespan assay statistics. Detailed data and statistical analyses of all lifespan assays and repeats thereof performed throughout this study.

File Name: Supplementary Data 2

File Type: Excel Workbook (\*.xlsx)

Description: *C. elegans* RNA-Seq data. Genes differentially overexpressed in *grh-1* OEx vs. wild-type nematodes with *P*-value < 0.05, as identified by RNA-Seq.

File Name: Supplementary Data 3

File Type: Excel Workbook (\*.xlsx)

Description: GRH-1 DNA-binding sites analysis. GRH-1 binding sites in the predicted promoters of the differentially overexpressed genes listed in Supplementary Data 2, as determined using the FIMO algorithm from the MEME Suite and the BiocManager::TFBSTools function in R. Genes in the MAP kinase pathway are highlighted in red font.

File Name: Supplementary Data 4

File Type: Excel Workbook (\*.xlsx)

Description: Primary compound screening results. Results of the primary screening of all 2,560 compounds from "The Spectrum Collection" on the GRHL and ARE/NRF2 luciferase reporter cell lines.

File Name: Supplementary Data 5

File Type: Excel Workbook (\*.xlsx)

Description: Human GRHL1-interacting proteins. All proteins selectively co-purifying with 3xFLAG-6xHis tagged wild-type human GRHL1, as detected by mass spectrometry.

File Name: Supplementary Data 6

File Type: Portable Document Format (\*.pdf)

Description: Annotated MS/MS spectra of GRHL1 post-translational modifications associated with papaverine treatment. MS/MS spectra of all GRHL1<sup>WT-TAG</sup> peptides corresponding to post-translational modifications exclusively identified in papaverine-treated samples according to PEAKS X search engine results.

File Name: Supplementary Data 7

File Type: Portable Document Format (\*.pdf)

Description: XICs of GRHL1 post-translational modifications associated with papaverine treatment. Extracted ion chromatograms (XICs) of the modified peptides identified only in the papaverine-treated samples and not in any of the DMSO control samples according to PEAKS X search engine results. The corresponding unmodified peptides are included, if identified. Raw files were imported into Skyline 21.1.0.146 (<https://doi.org/10.1074/mcp.m112.017707>), and the precursor MS1 traces were extracted ([M], [M+1], [M+2]). A peptide MS/MS library was build using the identification results from PEAKS and used as a reference for the selection of the correct MS1 traces.