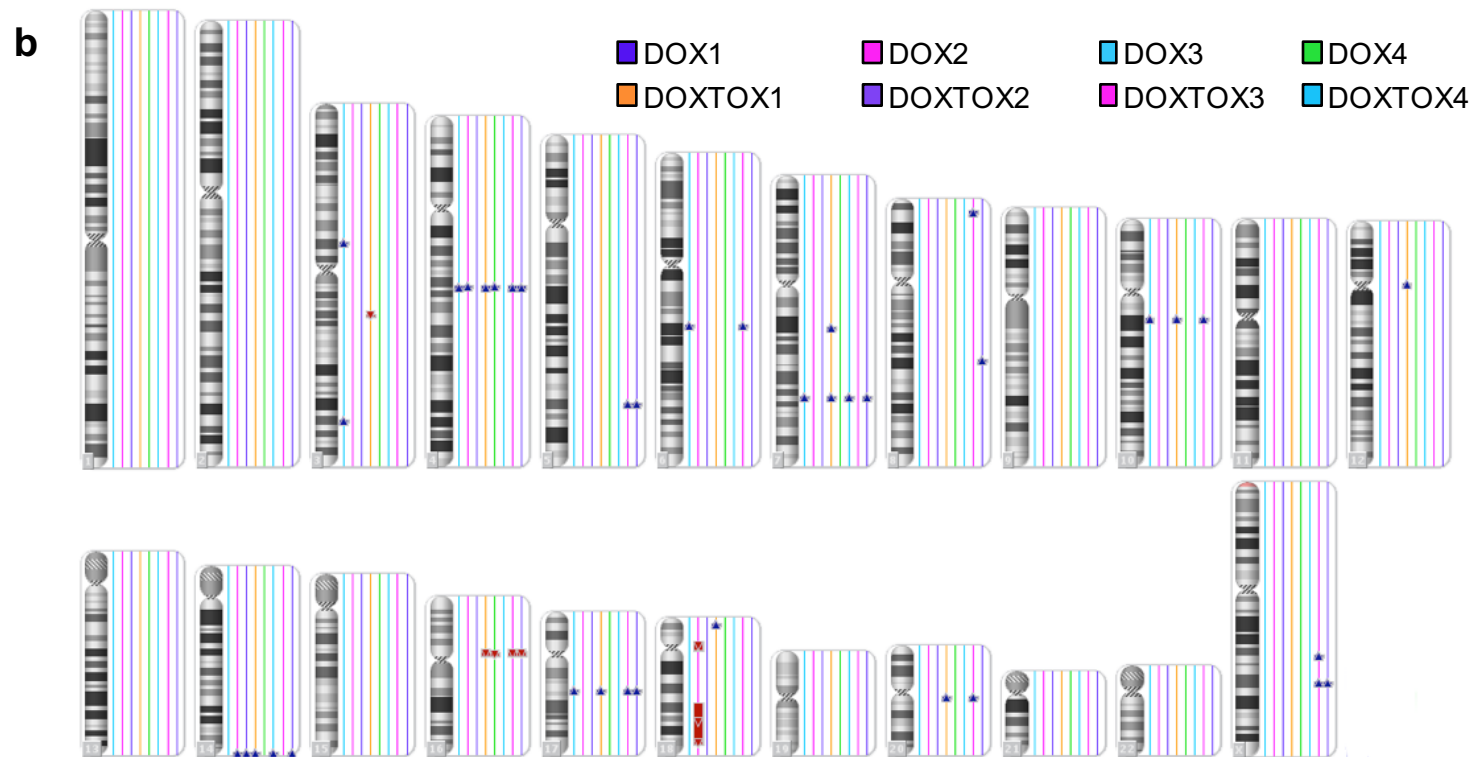
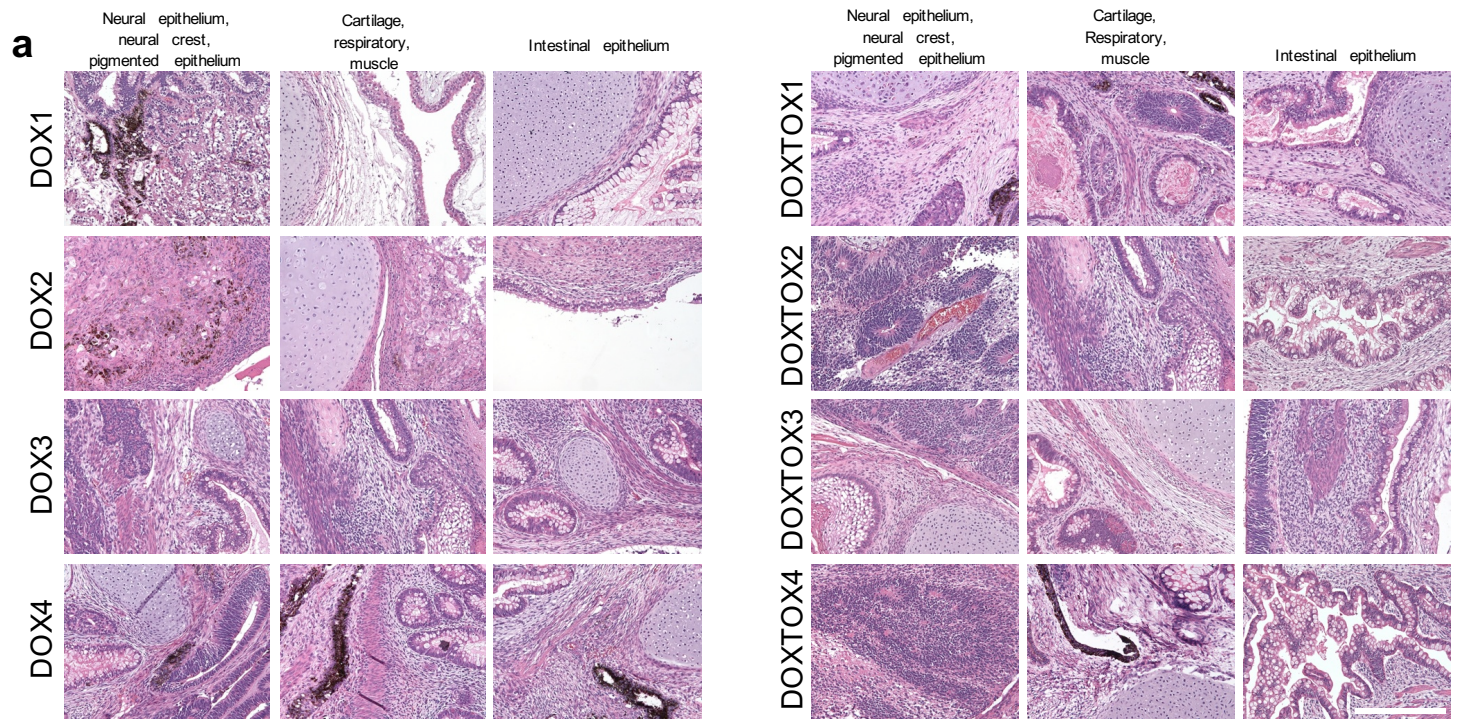
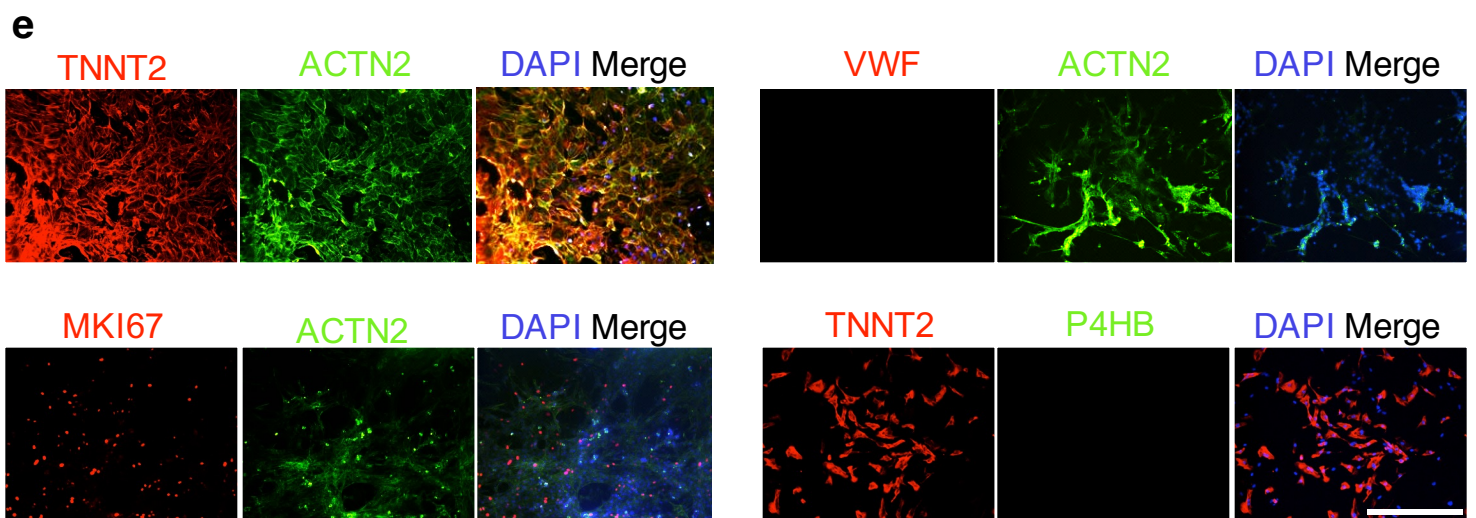
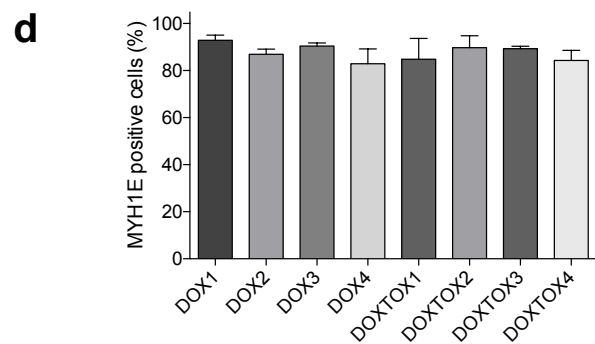
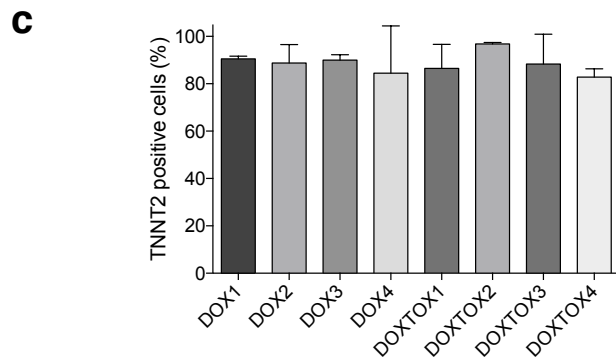
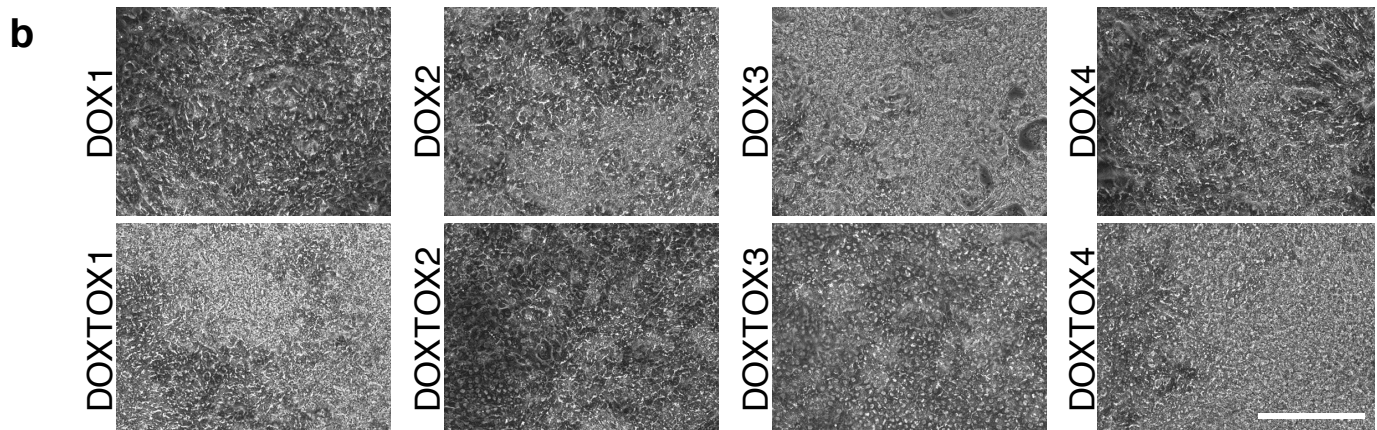
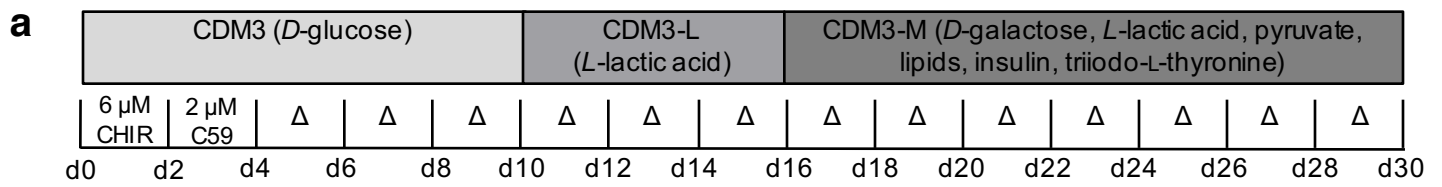
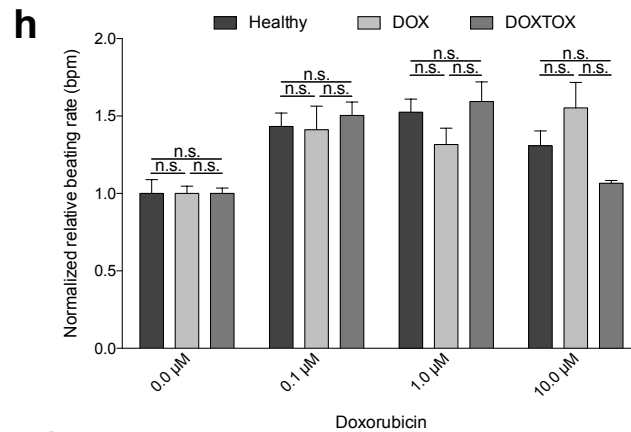
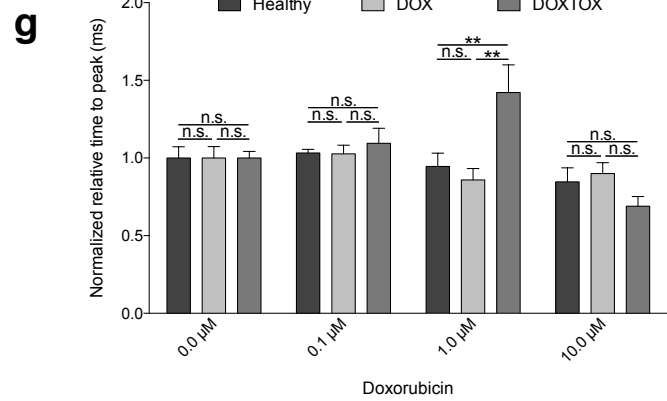
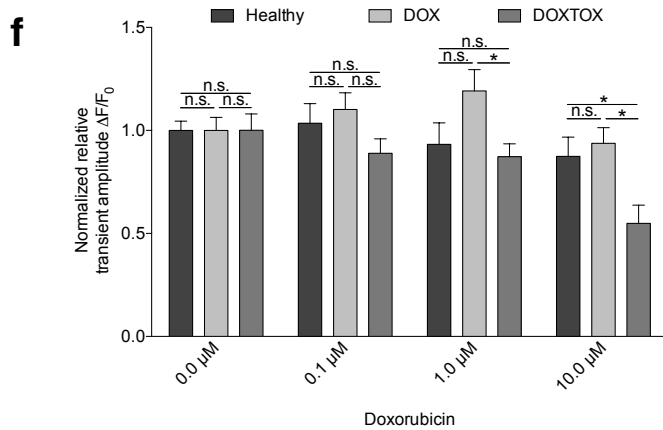
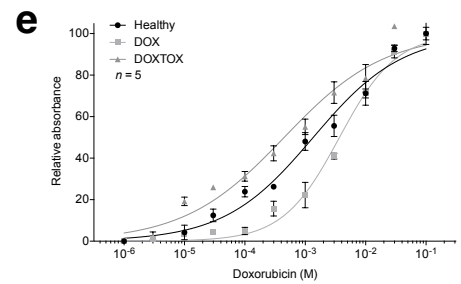
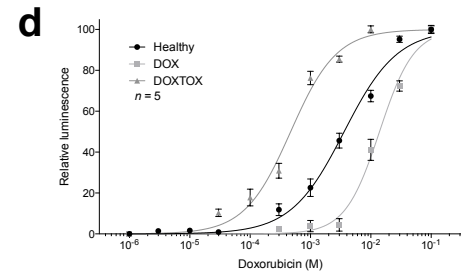
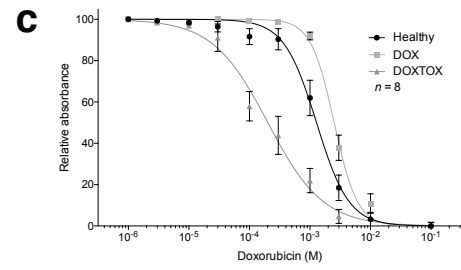
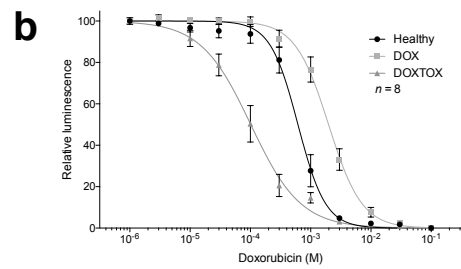
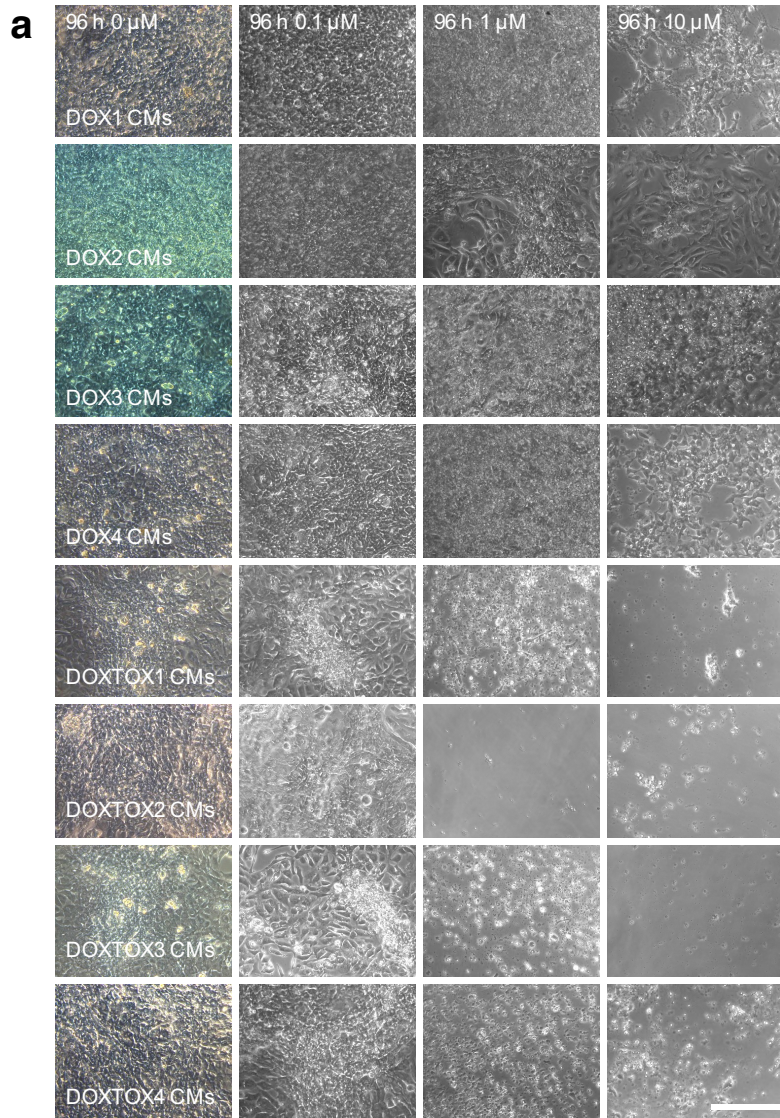


Supplementary Figure 1



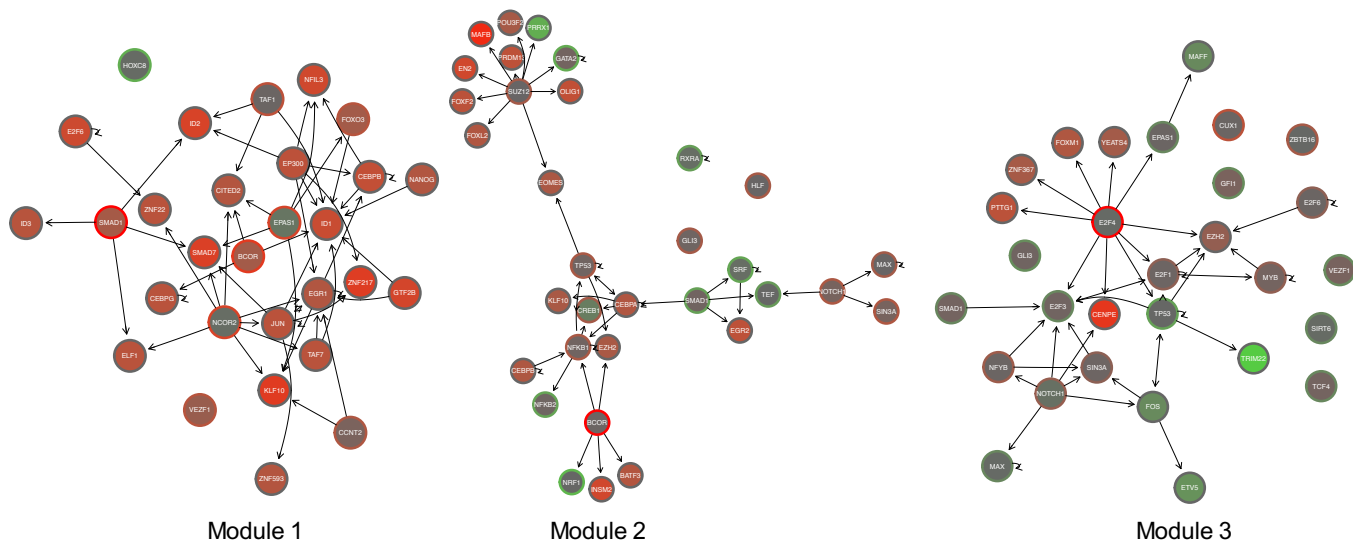
Supplementary Figure 2





Supplementary Figure 4

**a**



**b**

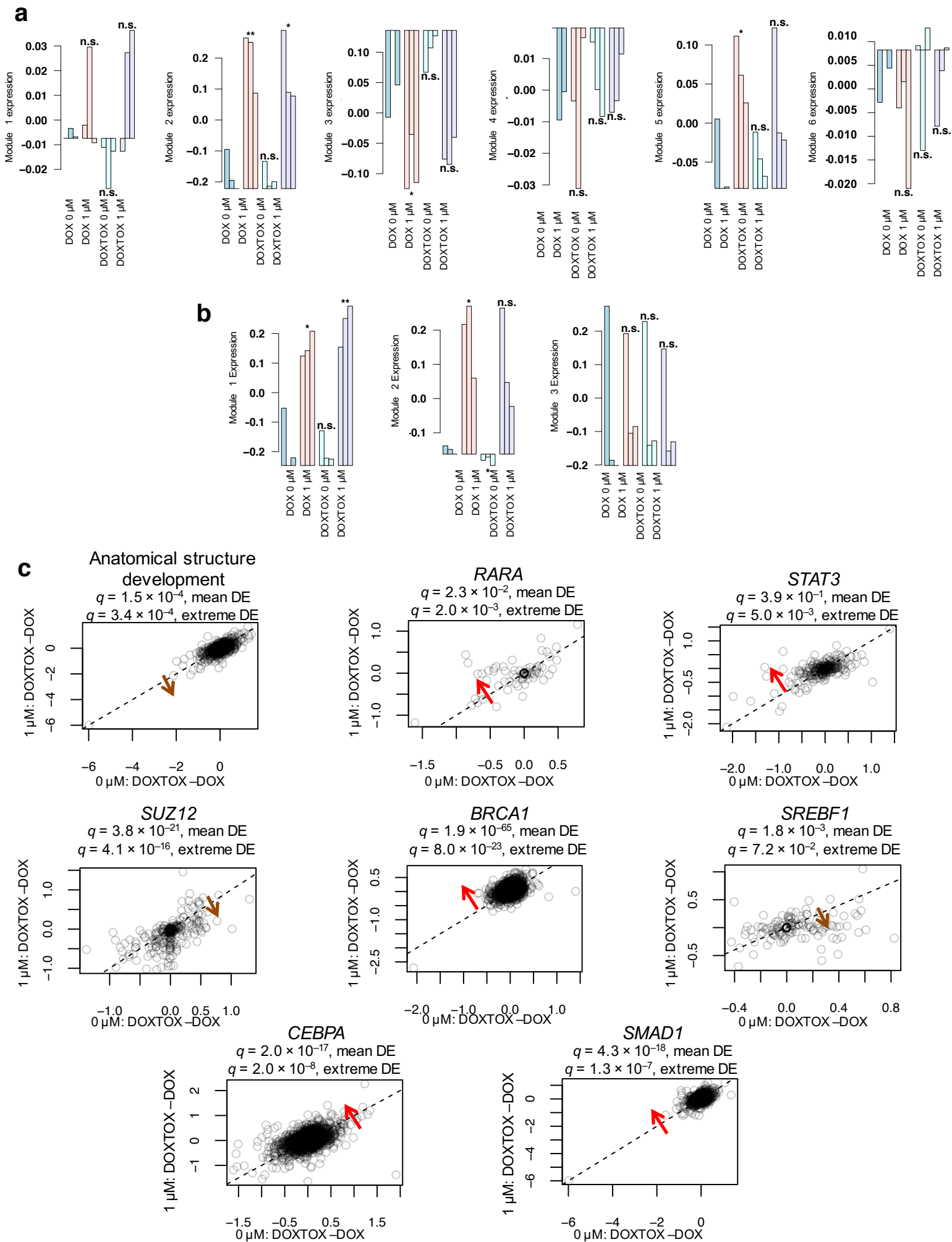
Module index	Module expression			Function annotation		
	Variance explained	PCC (P-value)	Gene ontology analysis summary	Significant transcription factors and q-values		TF function summary
1	41%	-0.9993 (9.4E-10)	Regulation of transcription; heart morphogenesis; apoptosis	(up) <i>BCOR</i> (6.9E-09); <i>NCOR2</i> (3.1E-05); <i>CCNT2</i> (3.1E-04); <i>EPAS1</i> (4.0E-04); <i>E2F4</i> (7.7E-04); <i>SMARCA4</i> (1.1E-03); <i>SMAD1</i> (2.2E-03); <i>TAF1</i> (2.2E-03); <i>JUND</i> (2.8E-03); <i>EP300</i> (3.4E-03); <i>VEZF1</i> (3.4E-03); <i>GATA2</i> (5.4E-03); <i>ZNF263</i> (5.4E-03); <i>BCL6</i> (6.0E-03); <i>TCF12</i> (6.0E-03); <i>SMARCB1</i> (7.2E-03); <i>MYC</i> (8.2E-03); <i>RAD21</i> (1.0E-02); <i>JUN</i> (1.1E-02); <i>TBP</i> (1.8E-02); <i>TFAP2C</i> (1.8E-02); <i>EGR1</i> (3.6E-02)	Oxidation/hypoxia stress response; inflammation	
2	39%	0.0344 (9.4E-1)	Epithelial to mesenchymal transition; nucleosome assembly	(up) <i>TAF7</i> (1.0E-04); <i>POU2F2</i> (1.0E-04); <i>SMARCA4</i> (1.2E-04); <i>SUZ12</i> (1.2E-04); <i>CTBP2</i> (1.4E-04); <i>TBP</i> (1.5E-04); <i>BCOR</i> (2.5E-04); <i>SMARCB1</i> (2.9E-04); <i>TP53</i> (3.3E-03); <i>BCLAF1</i> (4.5E-03); <i>GTF2F1</i> (8.3E-03); <i>STAT2</i> (2.5E-02); <i>TAF1</i> (3.5E-02) (down) <i>RELA</i> (3.9E-03)	DNA damage repair; apoptosis; Inflammation	
3	8%	0.1767 (6.8E-1)	Cell cycle control; DNA-damage response	(up) <i>E2F4</i> (1.4E-103); <i>NOTCH1</i> (2.7E-18); <i>E2F1</i> (4.7E-14); <i>NFYB</i> (3.9E-07); <i>TP53</i> (1.5E-05); <i>SIN3A</i> (3.3E-05); <i>MYB</i> (1.3E-04); <i>TCF3</i> (1.5E-04); <i>SPI1</i> (1.5E-04); <i>NCOR1</i> (9.6E-04); <i>NFYA</i> (3.5E-03); <i>ZNF76</i> (3.9E-03); <i>ZNF143</i> (5.1E-03); <i>E2F2</i> (8.9E-03); <i>SMAD1</i> (8.9E-03); <i>MYCN</i> (8.9E-03); <i>PBX1</i> (1.2E-02); <i>BCL6</i> (1.2E-02); (down) <i>TP53</i> (1.4E-13); <i>SPI1</i> (1.3E-03); <i>EGR1</i> (3.0E-03)	Cell cycle arrest; DNA damage response and apoptosis	

**c**

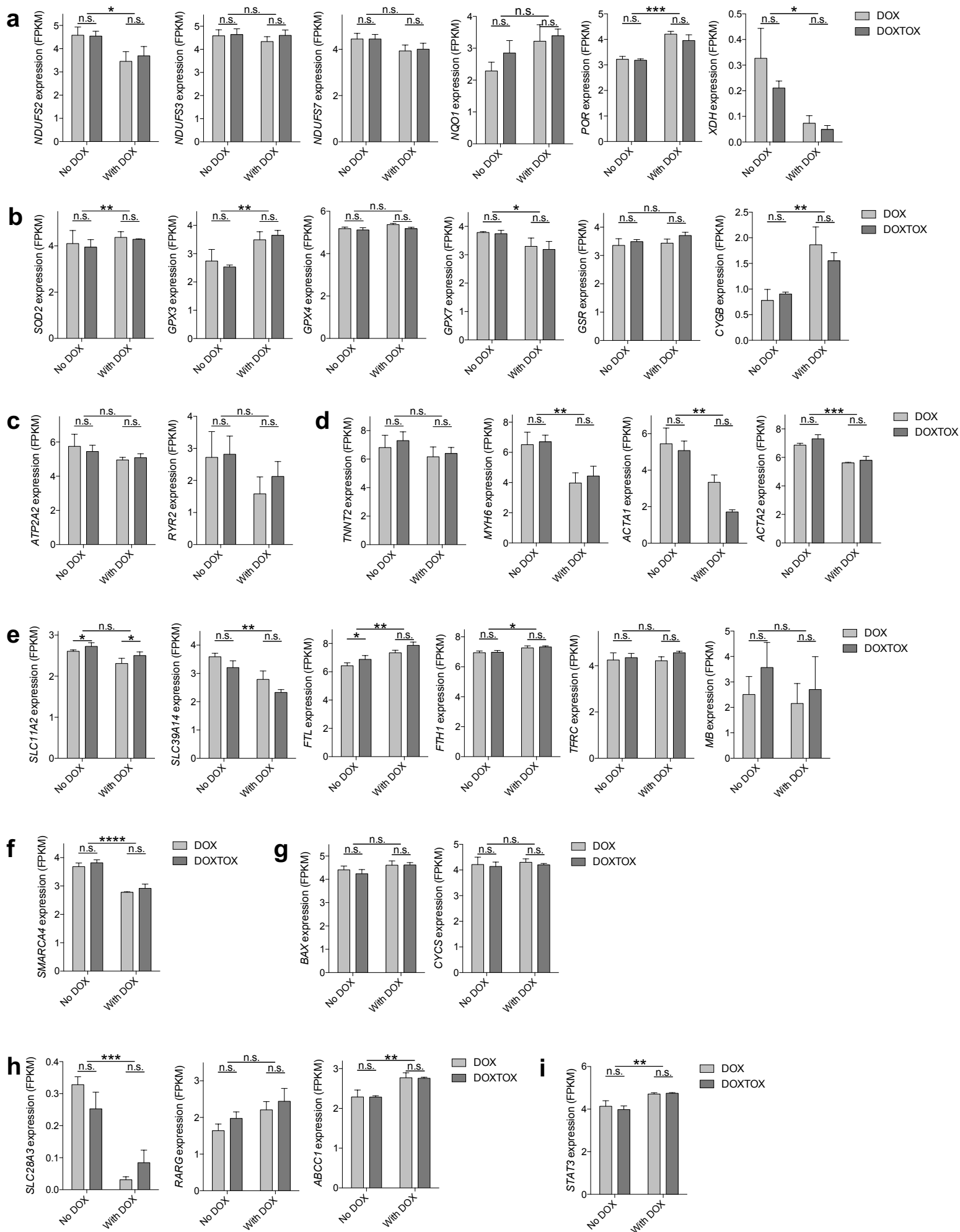
DOX vs. DOXTOX most highly differentially regulated genes after treatment with doxorubicin (at q-value < 0.05)

Gene symbol	DOX	DOXTOX	Log2 fold change	Test_stat	P-value	q-value	Note
<i>SFN</i>	127.3	4.4	-4.8	-3.1	0.00005	0.034925	A strong biomarker of cancer and is involved in cancer, downstream of p53
<i>CAPN6</i>	108.6	4.6	-4.6	-2.8	0.00005	0.034925	Calpains are ubiquitous, well-conserved family of calcium-dependent cysteine proteases. Inhibits apoptosis. Calpains have been implicated in neurodegenerative processes, as their activation can be triggered by calcium influx and oxidative stress. The protein may play a role in tumor formation by inhibiting apoptosis and promoting angiogenesis
<i>OLR1</i>	15.0	0.6	-4.5	-2.3	0.00005	0.034925	This gene encodes a low density lipoprotein receptor that belongs to the C-type lectin superfamily. Mutations of this gene have been associated with myocardial infarction.
<i>CST6</i>	361.1	20.9	-4.1	-3.2	0.00005	0.034925	The type 2 cystatin proteins are a class of cysteine protease inhibitors found in a variety of human fluids and secretions, where they appear to provide protective functions. This gene encodes a cystatin from the type 2 family, which is down-regulated in metastatic breast tumor cells as compared to primary tumor cells. Loss of expression is likely associated with the progression of a primary tumor to a metastatic phenotype.
<i>C1orf116</i>	4.6	0.3	-4.1	-1.9	0.00005	0.034925	NA
<i>TMEM40</i>	16.7	1.1	-3.9	-2.0	0.00005	0.034925	NA
<i>COMP</i>	22.2	1.5	-3.9	-2.4	0.00005	0.034925	The protein encoded by this gene is a noncollagenous extracellular matrix (ECM) protein. It consists of five identical glycoprotein subunits, each with EGF-like and calcium-binding (thrombospondin-like) domains.
<i>KRT7</i>	411.1	28.5	-3.8	-1.9	0.00005	0.034925	The protein encoded by this gene is a member of the keratin gene family. The type II cytokeratins consist of basic or neutral proteins which are arranged in pairs of heterotypic keratin chains coexpressed during differentiation of simple and stratified epithelial tissues. This type II cytokeratin is specifically expressed in the simple epithelia lining the cavities of the internal organs and in the gland ducts and blood vessels.
<i>SPP1</i>	114.6	13.0	-3.1	-1.7	0.00005	0.034925	The protein encoded by this gene is involved in the attachment of osteoclasts to the mineralized bone matrix. The encoded protein is secreted and binds hydroxyapatite with high affinity. The osteoclast vitronectin receptor is found in the cell membrane and may be involved in the binding to this protein. This protein is also a cytokine that upregulates expression of interferon-gamma and interleukin-12
<i>ALDH1A3</i>	59.6	7.0	-3.1	-2.0	0.00005	0.034925	This gene encodes an aldehyde dehydrogenase enzyme that uses retinal as a substrate.
<i>MYH14</i>	20.8	2.7	-3.0	-2.0	0.00005	0.034925	This gene encodes a member of the myosin superfamily. The protein represents a conventional non-muscle myosin
<i>NIPAL4</i>	17.6	2.4	-2.9	-1.7	0.00005	0.034925	This gene likely encodes a membrane receptor. Mutations in this gene have been associated with autosomal recessive congenital ichthyosis
<i>TINAGL1</i>	67.8	11.5	-2.6	-2.1	0.00005	0.034925	The protein encoded by this gene is similar in sequence to tubulointerstitial nephritis antigen, a secreted glycoprotein that is recognized by antibodies in some types of immune-related tubulointerstitial nephritis.
<i>IRF6</i>	14.5	2.8	-2.4	-1.6	0.00005	0.034925	This gene encodes a member of the interferon regulatory transcription factor (IRF) family.
<i>SOD3</i>	45.6	10.0	-2.2	-1.8	0.00005	0.034925	This gene encodes a member of the superoxide dismutase (SOD) protein family. SODs are antioxidant enzymes that catalyze the conversion of superoxide radicals into hydrogen peroxide and oxygen, which may protect the brain, lungs, and other tissues from oxidative stress
<i>S100A4</i>	198.3	44.5	-2.2	-1.6	0.00005	0.034925	The protein encoded by this gene is a member of the S100 family of proteins containing 2 EF-hand calcium-binding motifs. S100 proteins are localized in the cytoplasm and/or nucleus of a wide range of cells, and involved in the regulation of a number of cellular processes such as cell cycle progression and differentiation.
<i>OLFML3</i>	11.5	54.0	2.2	1.9	0.00005	0.034925	NA
<i>FREM1</i>	1.2	6.2	2.3	1.6	0.00005	0.034925	This gene encodes a basement membrane protein that may play a role in craniofacial and adrenal development. Mutations in this gene have been associated with bifid nose with or without anorectal and adrenal anomalies.
<i>MB</i>	15.3	81.0	2.4	1.6	0.00005	0.034925	This gene encodes a member of the globin superfamily and is expressed in skeletal and cardiac muscles. The encoded protein is a haemoprotein contributing to intracellular oxygen storage and transcellular facilitated diffusion of oxygen.
<i>DLK1</i>	18.0	187.4	3.4	3.0	0.00005	0.034925	This gene encodes a transmembrane protein containing six epidermal growth factor repeats. The protein is involved in the differentiation of several cell types, including adipocytes; it is also thought to be a tumor suppressor.
<i>GABRP</i>	1.7	28.4	4.0	1.8	0.00005	0.034925	The gamma-aminobutyric acid (GABA) A receptor is a multisubunit chloride channel that mediates the fastest inhibitory synaptic transmission in the central nervous system. The subunit encoded by this gene is expressed in several non-neuronal tissues including the uterus and ovaries.
<i>KRTAP3-1</i>	3.3	0.0	NA		0.00005	0.034925	NA

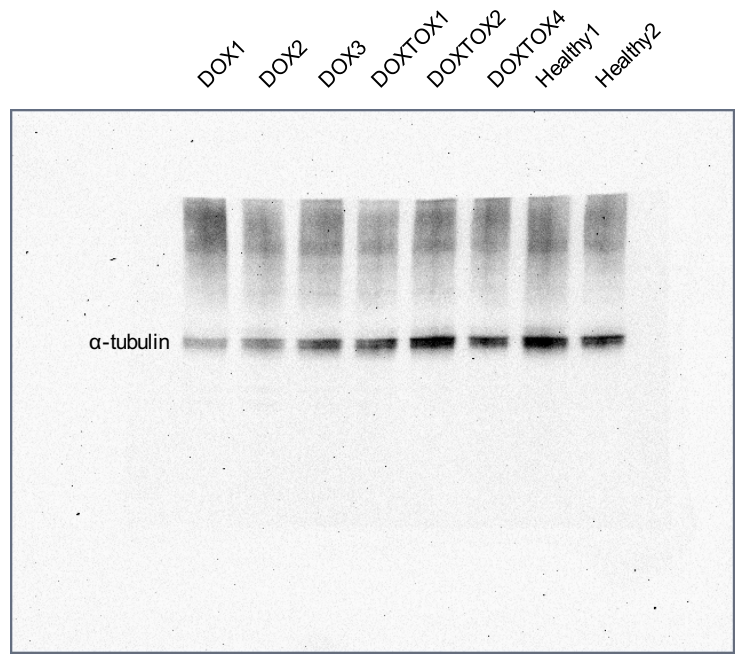
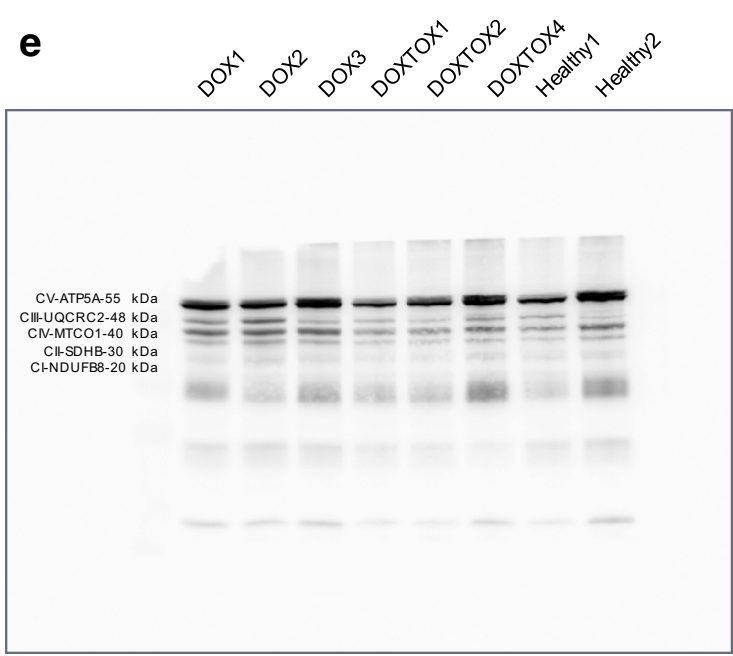
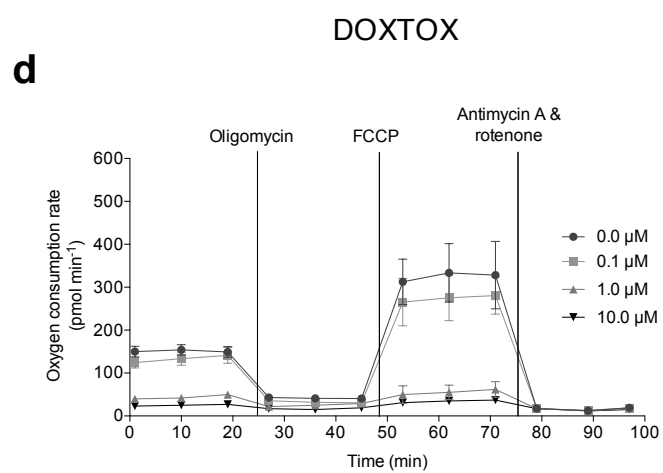
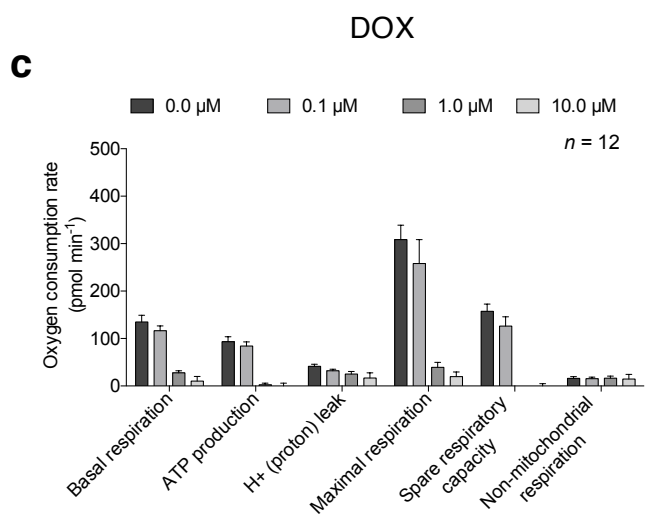
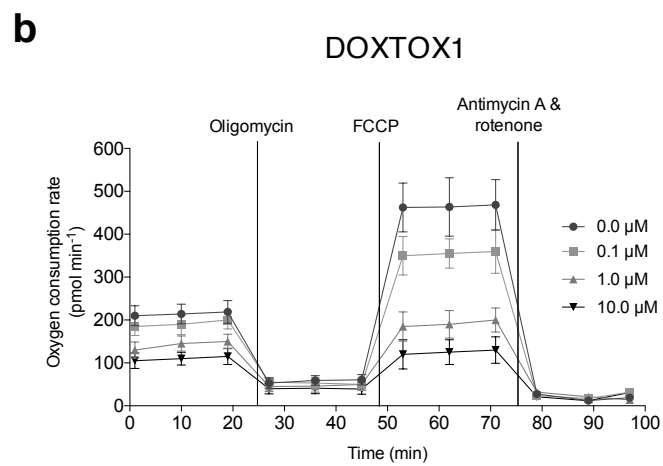
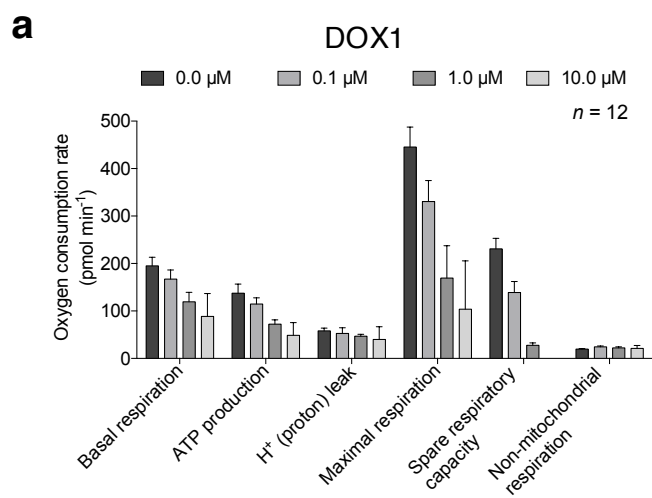
Supplementary Figure 5



Supplementary Figure 6

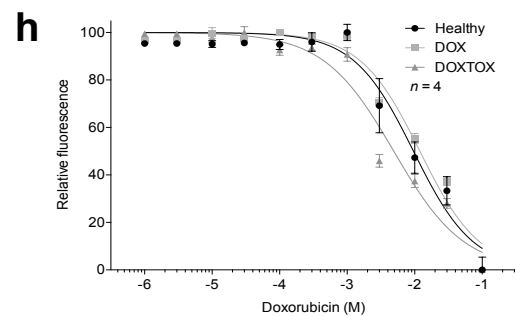
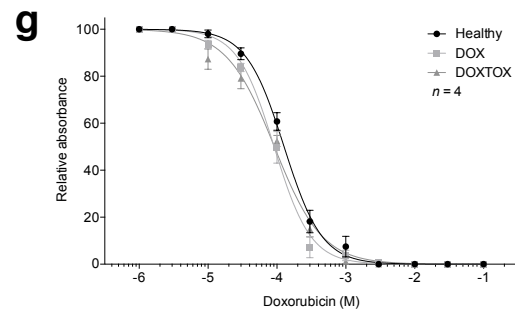
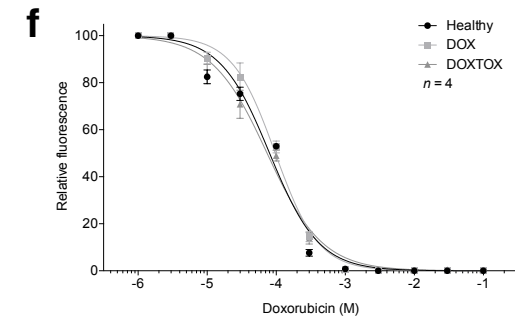
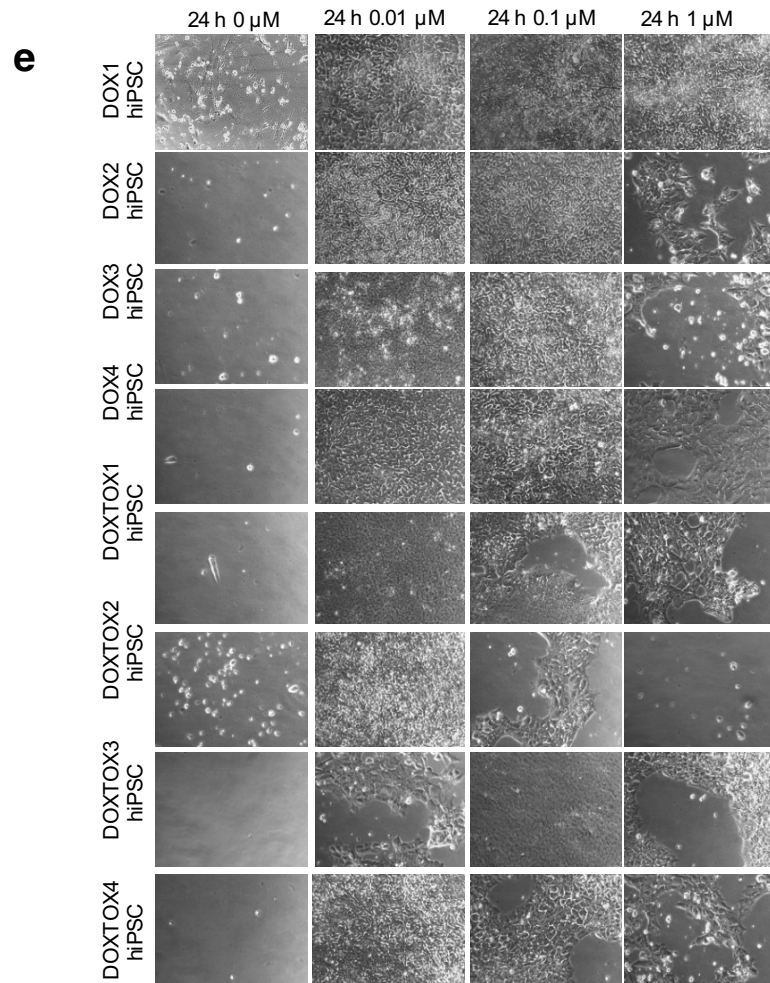
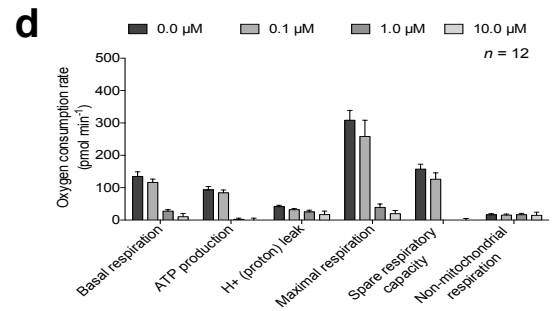
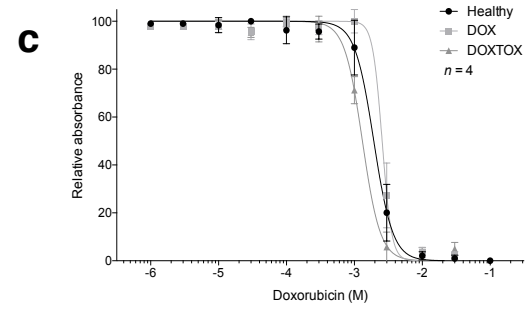
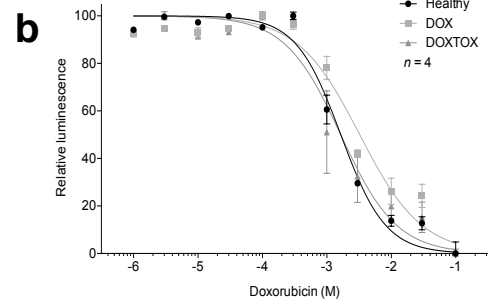
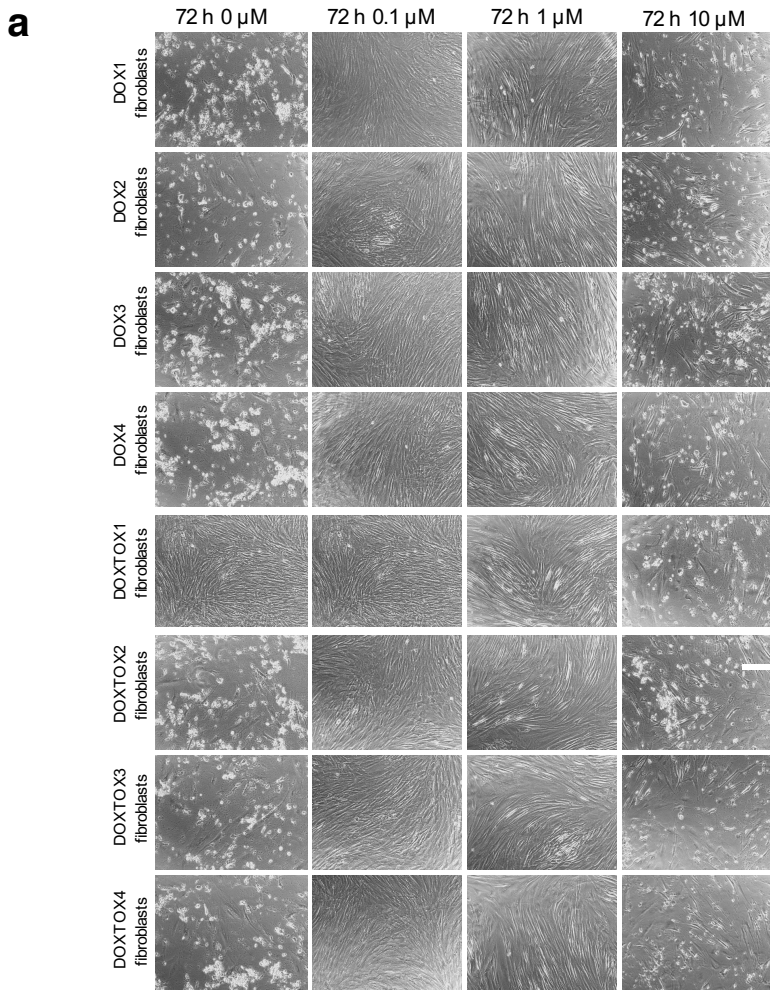


**Supplementary Figure 7**



Supplementary Figure 8





Supplementary Figure 9