

SUPPLEMENTAL MATERIALLiu et al., <http://www.jem.org/cgi/content/full/jem.20151248/DC1>**Table S1. Comparison of macrophage-specific induced genes common to all four drugs to those genes induced by in vitro stimuli**

In vitro stimulus	Reference list size	Overlap with macrophage-specific commonly induced list	Overlap by random chance	Overlap significance
Acid stress ^a	291	28	6	P < 0.001
Nutrient starvation ^b	440	27	9	P < 0.001
Oxidative stress (H ₂ O ₂) ^c	319	23	7	P < 0.001
NO/CO/DosR-dependent hypoxia ^d	50	18	1	P < 0.001
SDS-mediated membrane damage ^e	211	27	5	P < 0.001
Triton X-100-mediated membrane damage ^f	73	22	3	P < 0.001

^aData from Rohde et al. (2007).^bData from Betts et al. (2002) and Hampshire et al. (2004).^cData from Schnappinger et al. (2003) and Voskuil et al. (2011).^dData from Sherman et al. (2001), Ohno et al. (2003), Park et al. (2003), Shiloh et al. (2008), Voskuil et al. (2003), and Kumar et al. (2008).^eData from Manganelli et al. (2001) and He et al. (2006).^fData from He et al. (2006).**Table S2. Regulons that are commonly regulated by different frontline drugs in macrophages**

Regulator	Regulon size	Overlap with macrophage-specific commonly induced list	Overlap by random chance	Overlap significance
Rv3133c (DosR)	50	18	1	P < 0.001
Rv0757 (PhoP)	505	42	14	P < 0.001
Rv0981 (MprA)	275	34	7	P < 0.001
Rv1404	19	8	<1	P < 0.001
Rv3058c	136	13	3	P < 0.001
Rv0195	21	5	<1	P < 0.001
Rv3223c (SigH)	95	9	2	P < 0.001
Rv3676 (Crp)	43	6	1	P < 0.001
Rv3291c (IrpA)	7	3	<1	P < 0.001
Rv2760c (VapB42)	8	3	<1	P < 0.001
Rv0135c	2	2	<1	P < 0.001
Rv0023	489	21	11	P = 0.002
Rv0081	283	14	6	P = 0.004
Rv0445c (SigK)	33	4	1	P = 0.006

Regulon data for DosR, PhoP, and MprA are from Sherman et al. (2001), Ohno et al. (2003), Park et al. (2003), He et al. (2006), Kumar et al. (2008), Shiloh et al. (2008), Abramovitch et al. (2011), and Voskuil et al. (2003) and were obtained using regulator deletion strains; data for the rest regulators are from Rustad et al. (2014) and were generated using regulator overexpression strains. Regulons are ordered by overlap significance.

Table S3 is provided as an Excel file and lists macrophage-specific INH-induced genes.**Table S4 is provided as an Excel file and lists genes differentially regulated by individual drugs in macrophages.****Table S5 is provided as an Excel file and lists genes commonly regulated by different frontline drugs in macrophages.****Table S6 is provided as an Excel file and lists macrophage-specific commonly induced genes.****REFERENCES**

- Abramovitch, R.B., K.H. Rohde, F.F. Hsu, and D.G. Russell. 2011. *aprABC*: a *Mycobacterium tuberculosis* complex-specific locus that modulates pH-driven adaptation to the macrophage phagosome. *Mol. Microbiol.* 80:678–694. <http://dx.doi.org/10.1111/j.1365-2958.2011.07601.x>
- Betts, J.C., P.T. Lukey, L.C. Robb, R.A. McAdam, and K. Duncan. 2002. Evaluation of a nutrient starvation model of *Mycobacterium tuberculosis* persistence by gene and protein expression profiling. *Mol. Microbiol.* 43:717–731. <http://dx.doi.org/10.1046/j.1365-2958.2002.02779.x>
- Hampshire, T., S. Soneji, J. Bacon, B.W. James, J. Hinds, K. Laing, R.A. Stabler, P.D. Marsh, and P.D. Butcher. 2004. Stationary phase gene expression of *Mycobacterium tuberculosis* following a progressive nutrient depletion: a model for persistent organisms? *Tuberculosis (Edinb.)*. 84:228–238. <http://dx.doi.org/10.1016/j.tube.2003.12.010>
- He, H., R. Hovey, J. Kane, V. Singh, and T.C. Zahrt. 2006. MprAB is a stress-responsive two-component system that directly regulates expression of sigma factors SigB and SigE in *Mycobacterium tuberculosis*. *J. Bacteriol.* 188:2134–2143. <http://dx.doi.org/10.1128/JB.188.6.2134-2143.2006>

- Kumar, A., J.S. Deshane, D.K. Crossman, S. Bolisetty, B.S. Yan, I. Kramnik, A. Agarwal, and A.J. Steyn. 2008. Heme oxygenase-1-derived carbon monoxide induces the *Mycobacterium tuberculosis* dormancy regulon. *J. Biol. Chem.* 283:18032–18039. <http://dx.doi.org/10.1074/jbc.M802274200>
- Manganelli, R., M.I. Voskuil, G.K. Schoolnik, and I. Smith. 2001. The *Mycobacterium tuberculosis* ECF sigma factor σ^E : role in global gene expression and survival in macrophages. *Mol. Microbiol.* 41:423–437. <http://dx.doi.org/10.1046/j.1365-2958.2001.02525.x>
- Ohno, H., G. Zhu, V.P. Mohan, D. Chu, S. Kohno, W.R. Jacobs Jr., and J. Chan. 2003. The effects of reactive nitrogen intermediates on gene expression in *Mycobacterium tuberculosis*. *Cell. Microbiol.* 5:637–648. <http://dx.doi.org/10.1046/j.1462-5822.2003.00307.x>
- Park, H.D., K.M. Guinn, M.I. Harrell, R. Liao, M.I. Voskuil, M. Tompa, G.K. Schoolnik, and D.R. Sherman. 2003. Rv3133c/dosR is a transcription factor that mediates the hypoxic response of *Mycobacterium tuberculosis*. *Mol. Microbiol.* 48:833–843. <http://dx.doi.org/10.1046/j.1365-2958.2003.03474.x>
- Rohde, K.H., R.B. Abramovitch, and D.G. Russell. 2007. *Mycobacterium tuberculosis* invasion of macrophages: linking bacterial gene expression to environmental cues. *Cell Host Microbe.* 2:352–364. <http://dx.doi.org/10.1016/j.chom.2007.09.006>
- Rustad, T.R., K.J. Minch, S. Ma, J.K. Winkler, S. Hobbs, M. Hickey, W. Brabant, S. Turkarslan, N.D. Price, N.S. Baliga, and D.R. Sherman. 2014. Mapping and manipulating the *Mycobacterium tuberculosis* transcriptome using a transcription factor overexpression-derived regulatory network. *Genome Biol.* 15:502. <http://dx.doi.org/10.1186/s13059-014-0502-3>
- Schnappinger, D., S. Ehrt, M.I. Voskuil, Y. Liu, J.A. Mangan, I.M. Monahan, G. Dolganov, B. Efron, P.D. Butcher, C. Nathan, and G.K. Schoolnik. 2003. Transcriptional adaptation of *Mycobacterium tuberculosis* within macrophages: insights into the phagosomal environment. *J. Exp. Med.* 198:693–704. <http://dx.doi.org/10.1084/jem.20030846>
- Sherman, D.R., M. Voskuil, D. Schnappinger, R. Liao, M.I. Harrell, and G.K. Schoolnik. 2001. Regulation of the *Mycobacterium tuberculosis* hypoxic response gene encoding α -crystallin. *Proc. Natl. Acad. Sci. USA.* 98:7534–7539. <http://dx.doi.org/10.1073/pnas.121172498>
- Shiloh, M.U., P. Manzanillo, and J.S. Cox. 2008. *Mycobacterium tuberculosis* senses host-derived carbon monoxide during macrophage infection. *Cell Host Microbe.* 3:323–330. <http://dx.doi.org/10.1016/j.chom.2008.03.007>
- Voskuil, M.I., D. Schnappinger, K.C. Visconti, M.I. Harrell, G.M. Dolganov, D.R. Sherman, and G.K. Schoolnik. 2003. Inhibition of respiration by nitric oxide induces a *Mycobacterium tuberculosis* dormancy program. *J. Exp. Med.* 198:705–713. <http://dx.doi.org/10.1084/jem.20030205>
- Voskuil, M.I., I.L. Bartek, K. Visconti, and G.K. Schoolnik. 2011. The response of *Mycobacterium tuberculosis* to reactive oxygen and nitrogen species. *Front. Microbiol.* 2:105. <http://dx.doi.org/10.3389/fmicb.2011.00105>