Figure S1, Related to Figure 2

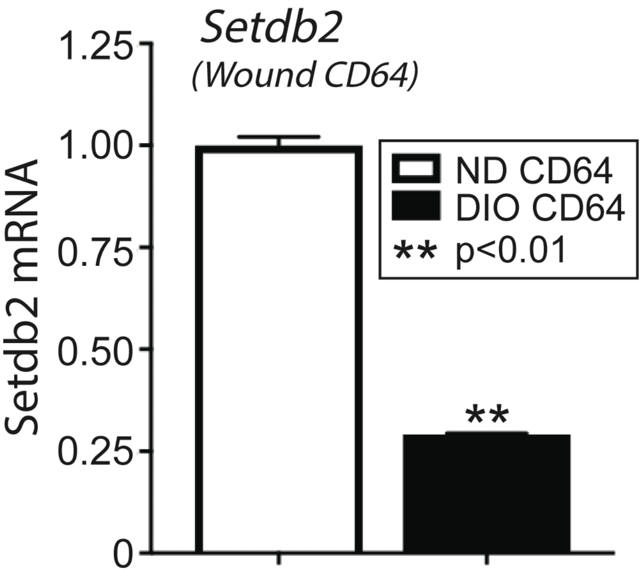

Figure S1. Setdb2 expression is decreased in diabetic CD64+ cells. Related to Figure 2. *Setdb2* expression quantified by qPCR in wound CD64+ cells MACs isolated from normal diet and DIO mice. (n =4 mice per group, replicated twice). $^*P < 0.05$, $^{**}P < 0.01$. Data are presented as the mean±SEM. Data were first analyzed for normal distribution and if data passed normality test, 2-tailed Student *t* test was used.

Figure S2, Related to Figure 3B

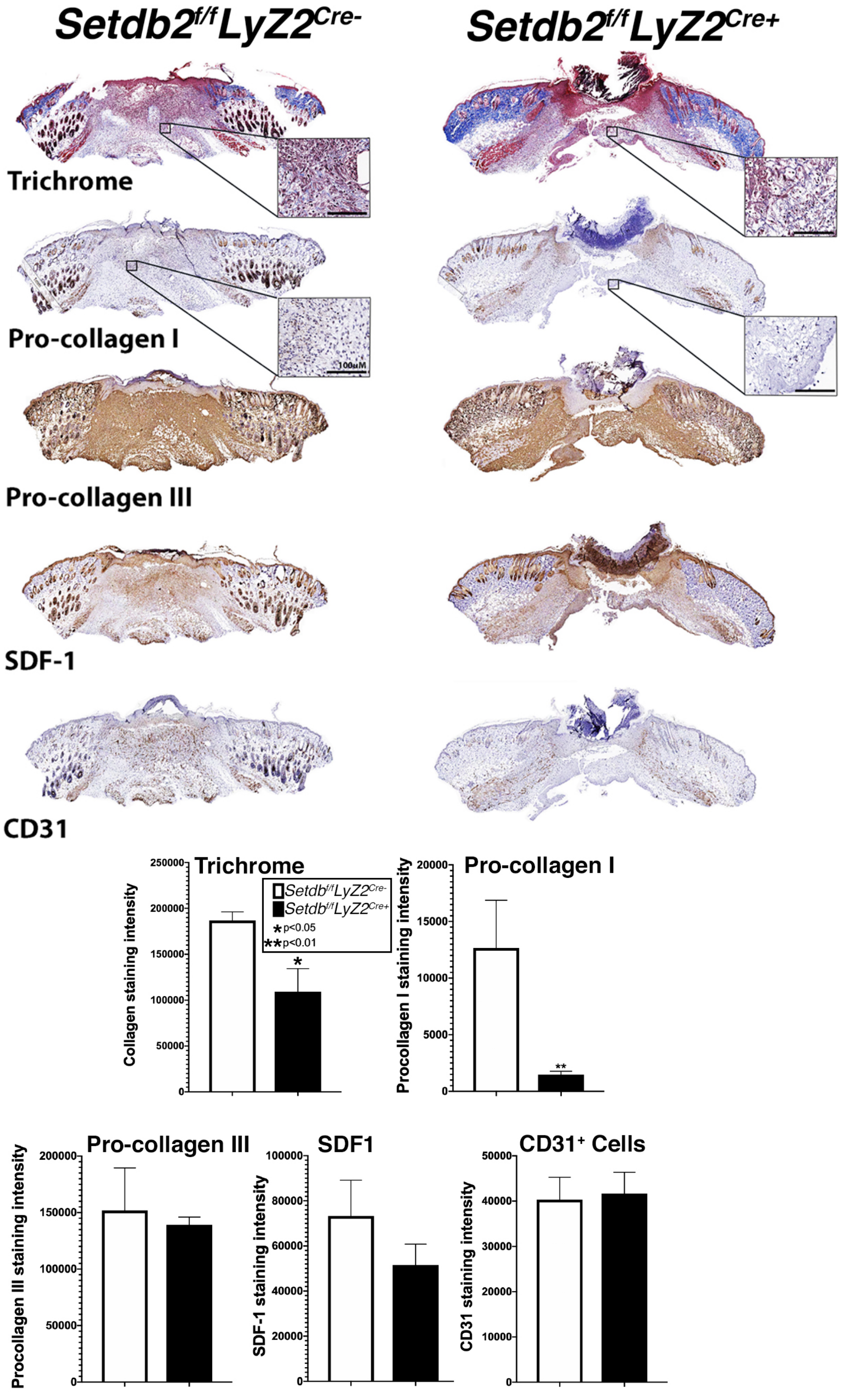

Figure S2. Loss of Setdb2 in wound macrophages decreases collagen deposition. Related to Figure 3. Wounds were stained with with Masson's Trichrome stain. Immunohistochemistry performed on Setdb2$^{f/f}$Lyz2^{Cre-} and Setdb2$^{f/f}$Lyz2^{Cre+} for pro-collagen-I, pro-collagen-II, SDF-1, and CD31. Representative images shown at 2X and 20X. Images were quantified ImageScope software. Data are presented as the mean±SEM. Data were first analyzed for normal distribution and if data passed normality test, 2-tailed Student t test was used.

Figure S3, Related to Figure 3

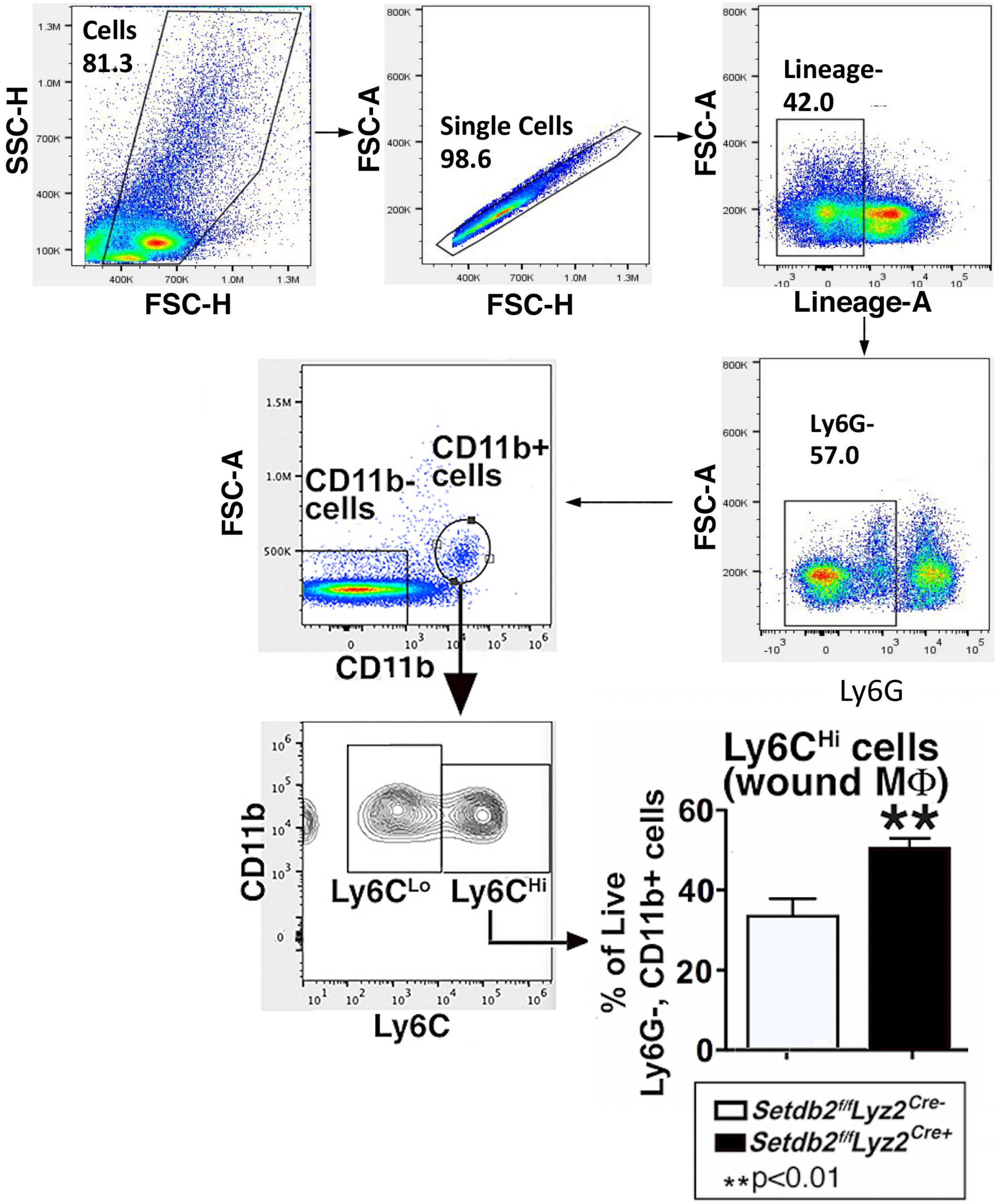

Figure S3. Gating strategy for *Setdb2*$^{f/f}$*LyZ*$^{Cre-}$ and *Setdb2*$^{f/f}$*LyZ*$^{Cre+}$ wound Mϕ. Related to Figure 3. Ly6C^{Hi} and Ly6C^{Lo} wound monocyte/macrophages from *Setdb2*$^{f/f}$*Lyz2*^{Cre} mice and littermate controls on day 5 (n = 6 mice per group) using the gating strategy demonstrated above to select single, live, Ly6G−, CD11b+ cells and stratify by Ly6C^{Hi} vs Ly6C^{Lo}.

Figure S4. Related to Figure 5

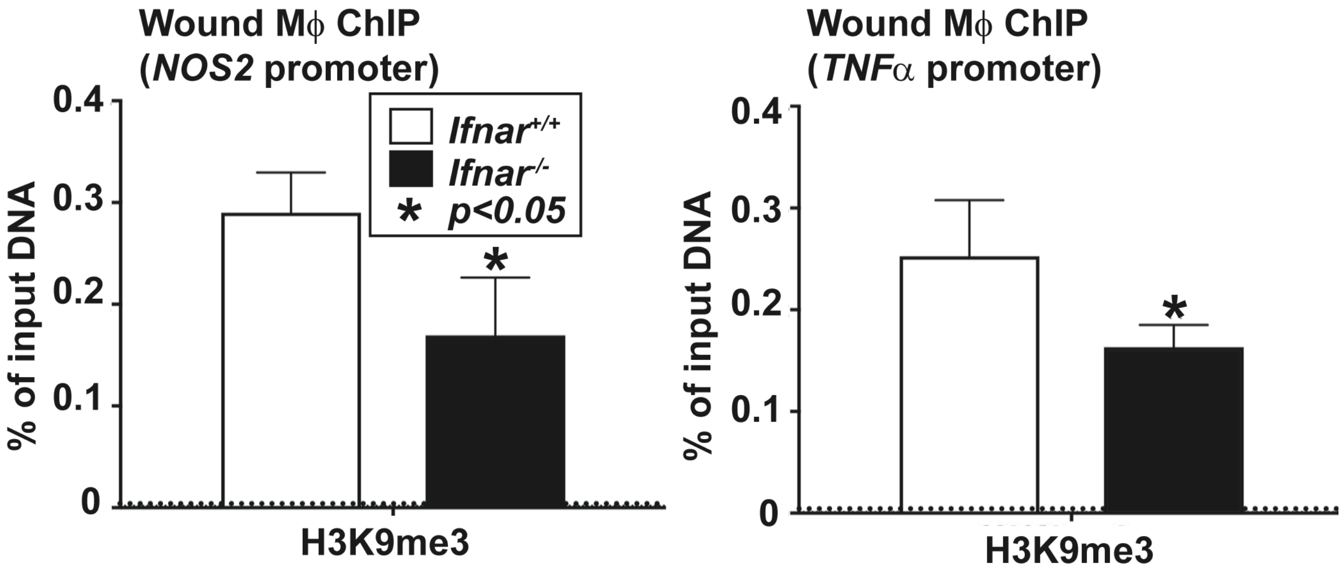

Figure S4. H3K9me3 is reduced at the promoters of TNFa and NOS2 in Interferon alpha-receptor-deficient mice. Related to Figure 5. ChIP analysis for H3K9me3 at the NF-κB binding site on the *TNFa* and *NOS2* promoters in wound macrophages from *Ifnar*$^{-/-}$ mice and *Ifnar*$^{+/+}$ controls (n = 6 mice per group). $^{*}P < 0.05$. Data are presented as the mean±SEM. Data were first analyzed for normal distribution and if data passed normality test, 2-tailed Student *t* test was used.

Figure S5. Related to Figure 5

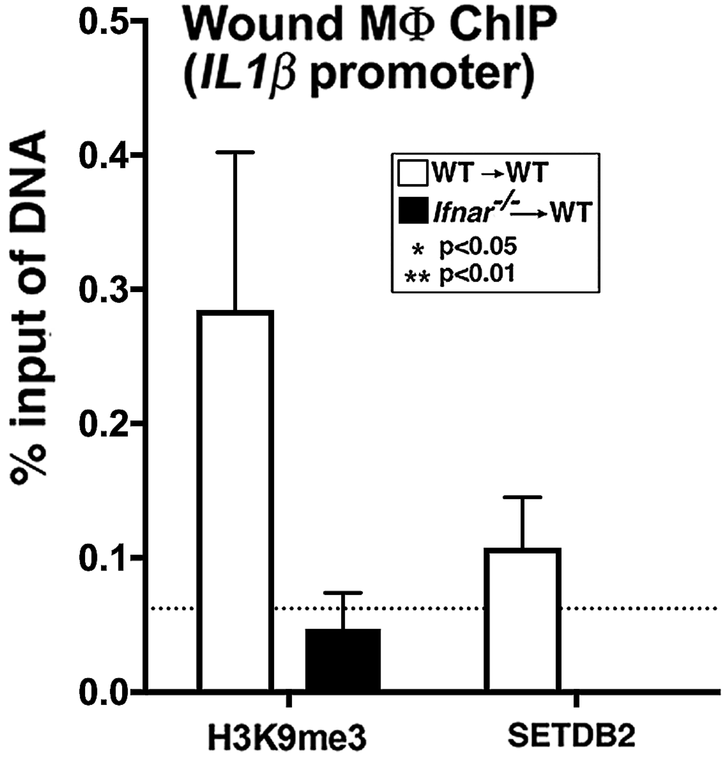

Figure S5. Setdb2 and H3K9me3 are reduced at the IL1B promoter in control BMT mice with Interferon-deficient bone marrow. Related to Figure 5. Bone marrow transplant was performed by injecting *Ifnar*$^{-/-}$ or *Ifnar*$^{+/+}$ control mice into irradiated *Ifnar*$^{+/+}$ control mice. Following reconstitution at 6 weeks, mice were wounded and wound macrophages isolated and ChIP analysis performed for H3K9me3 and Setdb2 at the NF-κB binding site on the *IL1β* promoter. (n=5 mice per group). Data are presented as the mean±SEM. Data were first analyzed for normal distribution and if data passed normality test, 2-tailed Student *t* test was used.

Figure S6. Related to Figure 6.

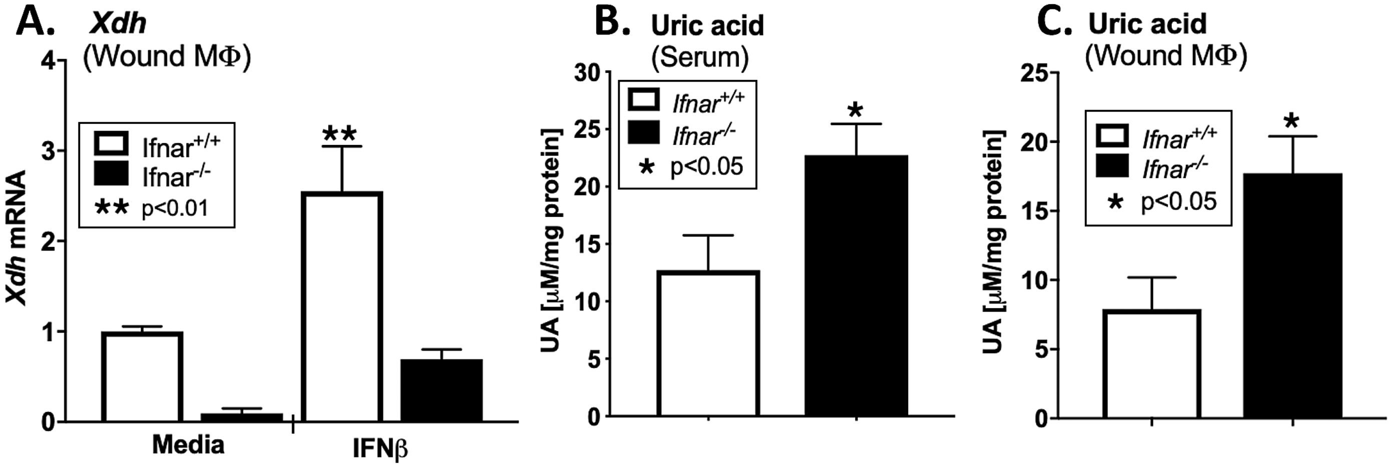

Figure S6. Loss of Ifnar alters uric acid metabolism. Related to Figure 6. (A) *Xdh* expression in wound macrophages from *Ifnar*$^{+/+}$ and *Ifnar*$^{-/-}$ mice stimulated *ex vivo* with IFNβ. (n = 5 mice per group). (B) UA levels in serum isolated from *Ifnar*$^{+/+}$ and *Ifnar*$^{-/-}$ (n = 5 per group mice). (C) UA levels in wound macrophages isolated on day 5 from *Ifnar*$^{+/+}$ and *Ifnar*$^{-/-}$ mice (n = 5 per group mice). All experiments ae representative of 3 independent experiments. *P < 0.05. Data are presented as the mean±SEM. Data were first analyzed for normal distribution and if data passed normality test, 2-tailed Student *t* test was used. For comparison between multiple groups, ANOVA followed by Newman–Keuls post hoc test was used.

Table SI. Expression patterns of distinct CME. Related to Figure 2A.

Superarray
(Wound MΦ)

Gene Symbol	Fold Up-regulation
Hdac9	4.4108
Esco2	3.9314
Pak1	2.7276
Prmt5	2.6556
Prmt7	2.4155
Rnf2	2.348
Aurka	2.2838
Mysm1	2.1832
Nek6	2.18
Prmt3	2.1775
Ciita	2.12
Setd6	2.1179
Rnf20	2.1121
Setdb2	2.0637
Usp16	2.0592
Smyd1	2.0159
Kat6b	2.0041
Hdac11	1.976
Usp21	1.9604
Hdac8	1.9588
Setd4	1.9552
Kat2b	1.9461
Setd2	1.9421
Esco1	1.9175
Aurkb	1.9147
Rps6ka3	1.9086
Dzip3	1.8945
Hdac7	1.8918
Hat1	1.8802
Kdm4c	1.8792
Prmt6	1.8401
Nsd1	1.839
Ncoa6	1.8257
Ash1l	1.8227
B2m	1.8028
Hsp90ab1	1.7951
Kmt2e	1.7773
Smyd3	1.7717
Ehmt1	1.7687
Kat6a	1.7623
Suv420h1	1.7483
Setd3	1.7422
Setd7	1.7264
Ube2a	1.7111
Setdb1	1.6955
Kdm1a	1.6906
Hdac2	1.6847
Suv39h1	1.6615
Kat7	1.6312
Ube2b	1.5957
Kmt2c	1.5811

Gene Symbol	Fold Down-regulation
Kdm5c	-1.0347
Kdm4a	-1.0766
RTC	-1.1325
Hdac10	-1.1446
Gapdh	-1.1529
Setd5	-1.1541
RTC	-1.1767
PPC	-1.2257
PPC	-1.2598
Dnmt3b	-1.2654
PPC	-1.2743
Dot1l	-1.4744
Ncoa3	-2.0448

Gusb	1.5716
Whsc1	1.5705
Hdac4	1.5591
Kat8	1.5512
Setd8	1.5468
Prmt1	1.5446
Hdac6	1.5141
Cdyl	1.5083
Setd1b	1.5081
Setd1a	1.4944
Atf2	1.4881
Ncoa1	1.4651
Kat2a	1.4298
Dnmt1	1.4218
Hdac5	1.4107
Csrp2bp	1.377
Rps6ka5	1.3609
Carm1	1.3532
Aurkc	1.3389
Prmt8	1.3389
MGDC	1.3389
Kdm5b	1.3212
Ehmt2	1.2698
Hdac1	1.2321
Hdac3	1.2255
Dnmt3a	1.21
Usp22	1.1765
Kat5	1.1718
Actb	1.1529
Kdm6b	1.0403
Prmt2	1.003

Table SII. Patient clinical characteristics. Related to Figure 2A.

Patient Characteristic	Non-diabetic	Diabetic
Age	73.3 (10.9)	64.3 (3.2)
Male	100%	50%
BMI	28.3 (1.6)	31.2 (1.8)
Prior Tobacco Use	66%	83%
Diabetes	N/A	100%
Hgb A1c	N/A	8.4 (0.3)
Hypertension	100%	83%
Hyperlipidemia	66%	83%
Coronary Artery Disease	33%	17%
Medications		
Insulin Dependent	N/A	33%
Oral Hyperglycemic	N/A	66%
Immunosuppressants	0%	0%

BMI, body mass index; Hgb A1c, hemoglobin A1C; N/A, non-applicable.
Continuous variables expressed as mean (SEM) and categorical variables expressed as percentages.

Table SIII. Cellular metabolites in BMDMs from *Setdb2*$^{f/f}$*Lyz2*$^{Cre-}$ and *Setdb2*$^{f/f}$*Lyz2*$^{Cre+}$. Related to Figure 6A.

Metabolite	*Setdb2*$^{f/f}$*Lyz2*$^{Cre-}$ (AUC)	*Setdb2*$^{f/f}$*Lyz2*$^{Cre+}$ (AUC)	P *value*
2,3-Phosphoglycerate	12264.4 (373.6)	14937.4 (1452.9)	0.1
Acetyl-CoA	11666.1 (617.0)	15198.9 (915.40	0.03
Acetylphosphate	9641.5 (2525.8)	9815.5 (1799.2)	1.0
Adenine	37385.2 (5072.8)	48955.0 (7718.8)	0.3
Adenosine	6930.2 (1263.7)	6628.8 (395.8)	0.8
ADP	303792.3 (13618.8)	336088.1 (31789.1)	0.4
ADP-D-glucose	17933.5 (555.4)	19762.8 (1266.3)	0.3
Alanine	138423.7 (11616.6)	148568.1 (3770.9)	0.5
Alpha-Ketoglutarate	134557.3 (5441.3)	161572.4 (5951.2)	0.03
AMP	36535.3 (889.2)	37799.0 (1177.3)	0.44
Arginine	1962154.2 (79268.6)	1550482.3 (69709.2)	0.02
Asparagine	1291131.6 (88990.2)	1155547.2 (44224.8)	0.24
Aspartate	775433.8 (27872.0)	713314.7 (21131.2)	0.15
ATP	3371707.0 (150695.5)	3857665.6 (165640.2)	0.10
Citrate/isocitrate	4030612.2 (54561.8)	4242428.5 (127266.7)	0.20
Citrulline	127288.8 (2851.1)	104508.8 (6183.3)	0.03
CMP	11535.7 (248.5)	10327.6 (1070.2)	0.33
CoA	12141.9 (620.7)	14527.3 (875.0)	0.09
Creatinine	68564.2 (772.3)	62910.6 (1673.3)	0.04
CTP	95089.1 (2656.7)	108691.4 (5446.3)	0.09
Deoxyuridine	39369.0 (8674.6)	33519.3 (5361.2)	0.60
D-Rib(ul)ose-5-phosphate	7522.6 (604.7)	7576.4 (537.5)	0.95
FAD	12043.9 (645.3)	15374.6 (1333.9)	0.09
Fructose 1,6-bisphosphate	128922.2 (8380.7)	156552.7 (9689.5)	0.10
GDP	34656.6 (3453.0)	35402.7 (2048.5)	0.86
Gluconate	256166.9 (10954.8)	256215.4 (5478.1)	1.00
Glucosamine-1-P/6-P	15747.8 (222.4)	16206.0 (729.1)	0.58
Glutamate	4240698.7 (53570.6)	4677222.9 (177424.6)	0.08
Glutamine	14796662.8 (256230.0)	12004518.4 (774345.5)	0.03
Glycerol-3-phosphate	364404.3 (10717.9)	407383.3 (30220.4)	0.25
Glycine	52364.1 (860.0)	37101.8 (2522.8)	0.00
GMP	4203.6 (360.7)	4041.1 (360.5)	0.77
GTP	279905.0 (24681.9)	311557.7 (14731.7)	0.33
Hexose	4932348.4 (95617.1)	3956330.4 (230380.5)	0.02
Hexose-phosphate	88195.9 (9573.5)	104568.5 (15411.8)	0.42
Histidine	1453472.2 (30401.4)	1286107.9 (81240.7)	0.13
Hypoxanthine	1074599.2 (18990.5)	1022677.2 (38369.0)	0.29
Itaconate	534140.9 (22753.8)	600555.7 (33011.2)	0.17
Lactate	257205.6 (38343.6)	123555.5 (29144.6)	0.05
Leucine/isoleucine	10880011.1 (188041.0)	8979095.2 (421703.3)	0.01
Lysine	551509.8 (9237.7)	438464.4 (27635.8)	0.02
Malate	1012820.9 (70171.8)	1076266.6 (55819.8)	0.52
Methionine	547756.7 (10523.8)	439877.3 (19703.9)	0.01
N-Acetyl-glucosamine-1-phosphate	18992.0 (508.0)	23580.6 (2095.8)	0.10
N-acetyl-neuraminic acid	205551.9 (15877.4)	150028.7 (13599.0)	0.06
NAD+	197655.8 (2564.5)	241769.9 (10478.8)	0.01
NADH	39244.9 (2200.0)	44054.1 (3808.3)	0.34
NADP+	18549.9 (1889.8)	19371.8 (2069.1)	0.78
NADPH	43435.7 (1316.0)	53003.6 (2679.6)	0.03
Oleic acid	621839.8 (22149.6)	557250.6 (23677.0)	0.12
Ornithine	591587.0 (40059.6)	446006.8 (17007.9)	0.03
Oxidized glutathione	177773.3 (15066.6)	175660.0 (6202.3)	0.90
Palmitic acid	4749700.2 (1176443.6)	4018057.9 (732496.0)	0.63
Pantothenate	709092.8 (29945.4)	629986.6 (27594.2)	0.12

Phenylalanine	1948009.5 (68490.7)	1600994.5 (66214.2)	0.02
Phenylpyruvate	44227.7 (555.8)	37699.9 (2177.1)	0.04
Phosphocreatine	156159.4 (5043.2)	212949.0 (16337.2)	0.03
Proline	674565.5 (4571.6)	556349.3 (26487.9)	0.01
PS_38:4	2208222.2 (619915.9)	3106456.6 (228782.7)	0.25
PS_40:6	1104232.3 (318782.6)	1559271.4 (114488.4)	0.25
Quinolinate	7404.5 (293.1)	6479.8 (396.7)	0.13
Reduced glutathione	2306735.3 (122951.3)	2921844.9 (301680.0)	0.13
Stearic acid	7754375.2 (2233283.2)	6633317.3 (1488361.1)	0.70
Succinate	150243.8 (6546.4)	131966.7 (9631.4)	0.19
Taurine	28775312.7 (720358.6)	32438746.8 (1340214.1)	0.07
Threonine	362845.8 (6225.7)	281224.2 (14847.8)	0.01
Tryptophan	728682.9 (29371.8)	597773.0 (22852.8)	0.02
Tyrosine	1801880.9 (42356.4)	1517693.2 (90224.4)	0.05
UDP-D-glucose	398227.9 (9344.3)	472761.4 (24687.8)	0.05
UDP-D-glucuronate	60377.7 (295.4)	73787.1 (5219.2)	0.06
UDP-N-acetyl-D-glucosamine	317893.3 (6863.9)	357699.3 (20176.2)	0.14
Uracil	4623.7 (2002.9)	1727.2 (610.3)	0.24
UTP	403819.4 (14138.7)	465197.8 (27293.9)	0.12
Valine	1080686.3 (13200.5)	892409.0 (38404.5)	0.01
Xanthine	327270.2 (5203.9)	240360.0 (17886.1)	0.01

AUC, area under the curve. Values expressed as mean (SEM) representing the mean of 3 independent samples.