SUPPORTING INFORMATION

Pyrazinoic acid inhibits mycobacterial coenzyme A biosynthesis by binding to aspartate decarboxylase PanD

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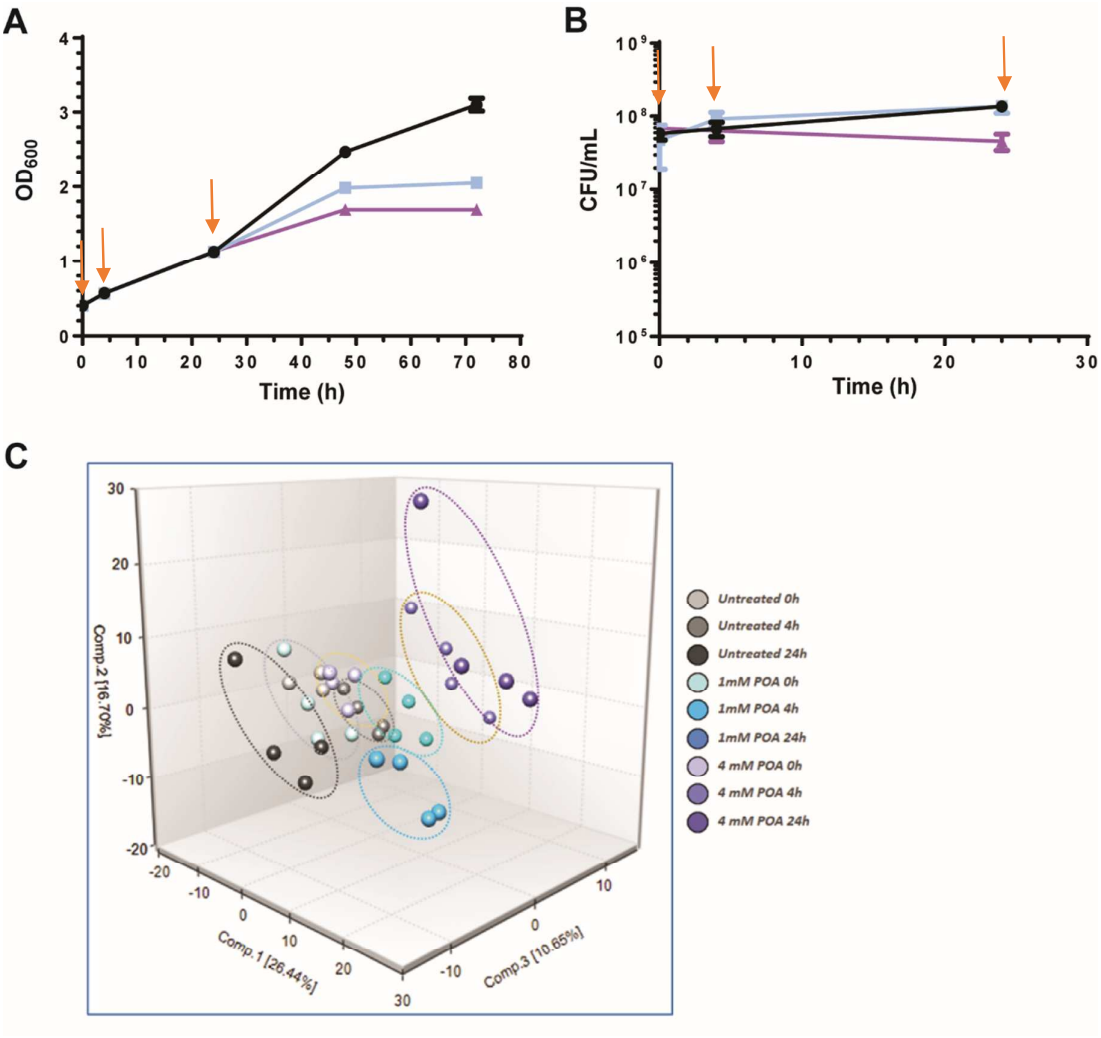

Figure S1. Effect of POA on the growth and metabolome of *M. bovis* BCG represented by (A) optical density at 600 nm (OD_{600}) and (B) colony forming units (CFU/mL) as a function of time. Treatment with no POA, 1 mM POA or 4 mM POA are represented by black circles, blue squares or purple triangles respectively. Arrows indicate time points at which samples were collected for metabolomics analyses. Experiment was carried out 4 times independently. Mean values and standard deviations are shown. (C) Principal Component Analysis (PCA) of metabolite profiles in *M. bovis* BCG treated with different concentrations of POA (0, 1 mM or 4 mM) at different time points (0, 4 and 24 hours). Data points represent 4 biological replicates under each condition.

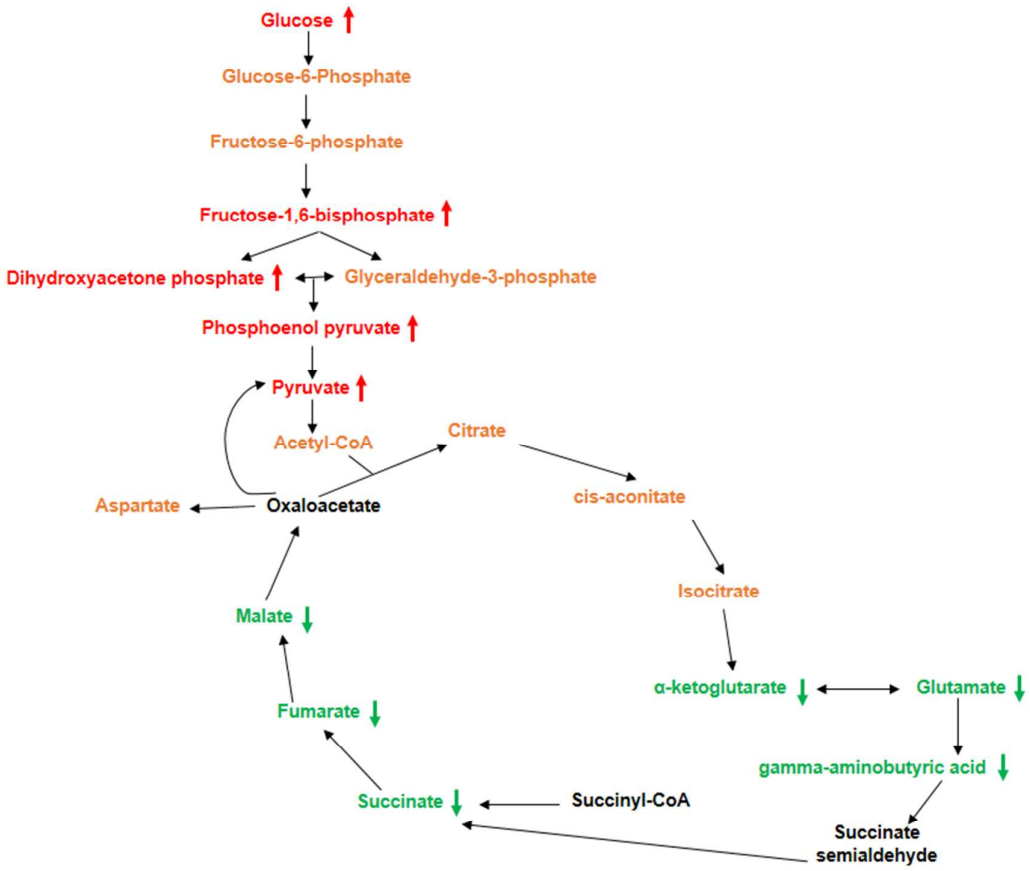

Figure S2. Schematic representation of the glycolytic pathway and tricarboxylic acid cycle indicating metabolites altered upon POA treatment. Upon 1 mM / 4 mM POA treatment for 24 hours, metabolites that are significantly increased are represented in red, while those that are significantly reduced are in green as compared to untreated controls (Table S1, ANOVA p-values < 0.05). Metabolites that are not significantly changed upon POA treatment are shown in orange while those that could not be identified in our analysis are in black.

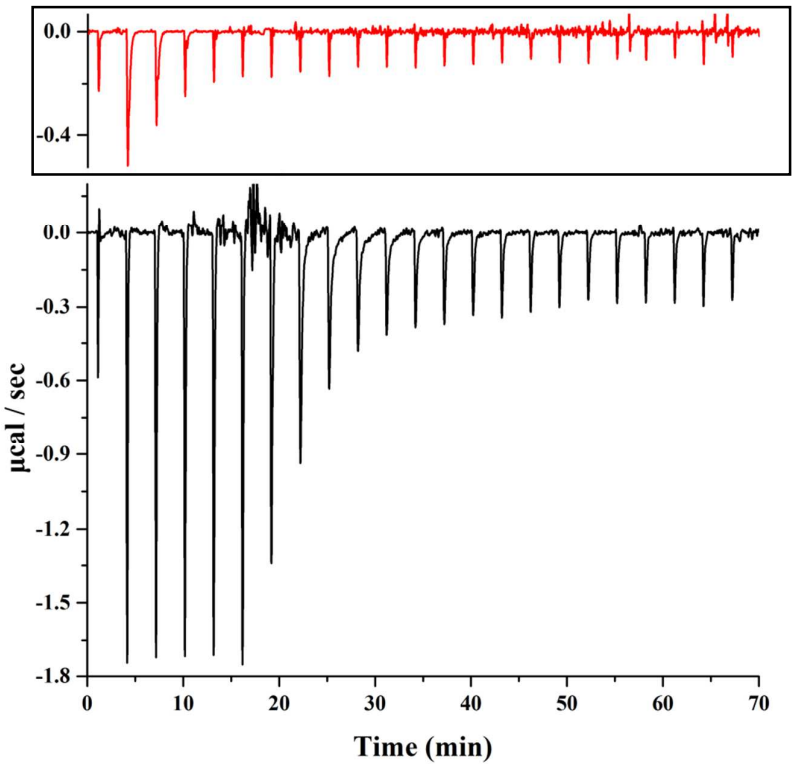

Figure S3. Binding affinity measurements for POA with $PanD_{WT}$ using ITC. The plot in the box shows the heat released due to titration of 2 mM POA against water which is taken as reference. The plot (black) shows the raw data of titration of $PanD_{WT}$ (in water) against 2 mM POA. It is revealed as representative ITC profile for the drugs used in this study. The net heat released due to binding of POA with $PanD_{WT}$ after subtraction of the reference is shown in Figure 4A (see Results part).

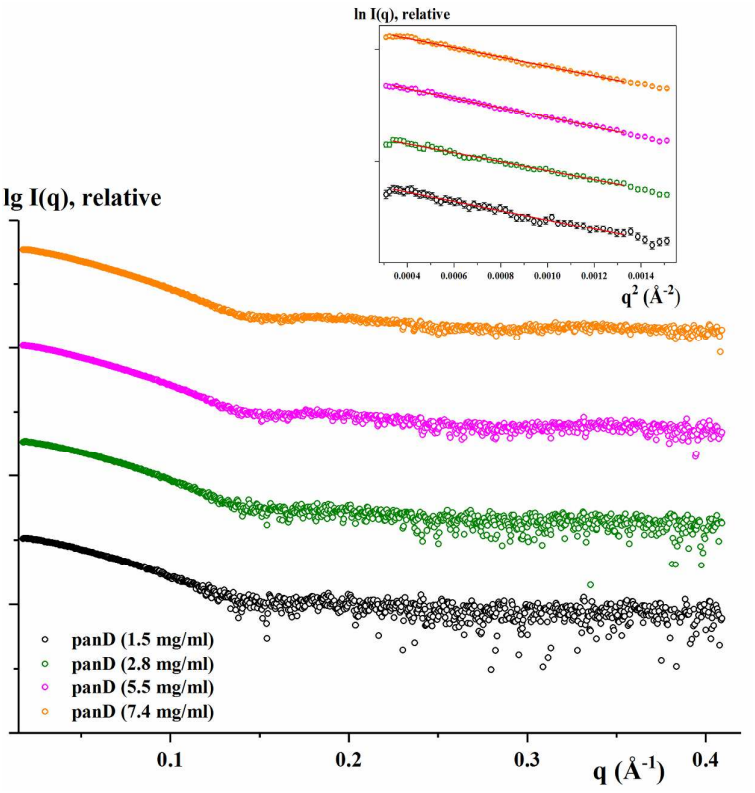

Figure S4. Solution X-ray scattering pattern (○) of $PanD_{WT}$ at 1.5 mg/mL (*black*), 2.8 mg/mL (*green*), 5.5 mg/mL (*magenta*) and 7.4 mg/mL (*orange*) concentration. (*Inset*) Guinier plots show linearity at all concentrations used, indicating no aggregation. The scattering profiles are offset for clarity by applying arbitrary scale factors.

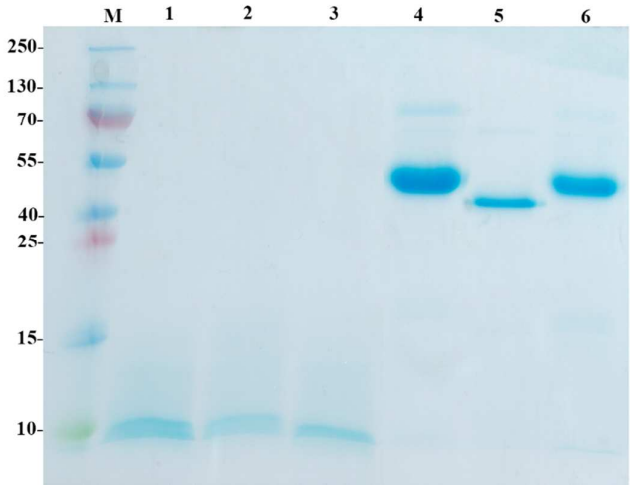

Figure S5. Verification of purified recombinant PanD proteins. SDS gel (17% total acrylamide and 0.4% crosslinked acrylamide) of the purified recombinant proteins $PanD_{WT}$, $PanD_{127TRASC131}$, and $PanD_{H21R}$, respectively. *Lane M* shows molecular weight markers. *Lane 1*, *2* and *3* shows recombinant $PanD_{WT}$, $PanD_{127TRASC131}$, and $PanD_{H21R}$ which were autoclaved in the presence of 1 mM DTT. *Lane 4*, *5* and *6* show the $PanD_{WT}$, $PanD_{127TRASC131}$, and $PanD_{H21R}$ which are loaded in the presence of 1 mM of DTT and the samples were not autoclaved.

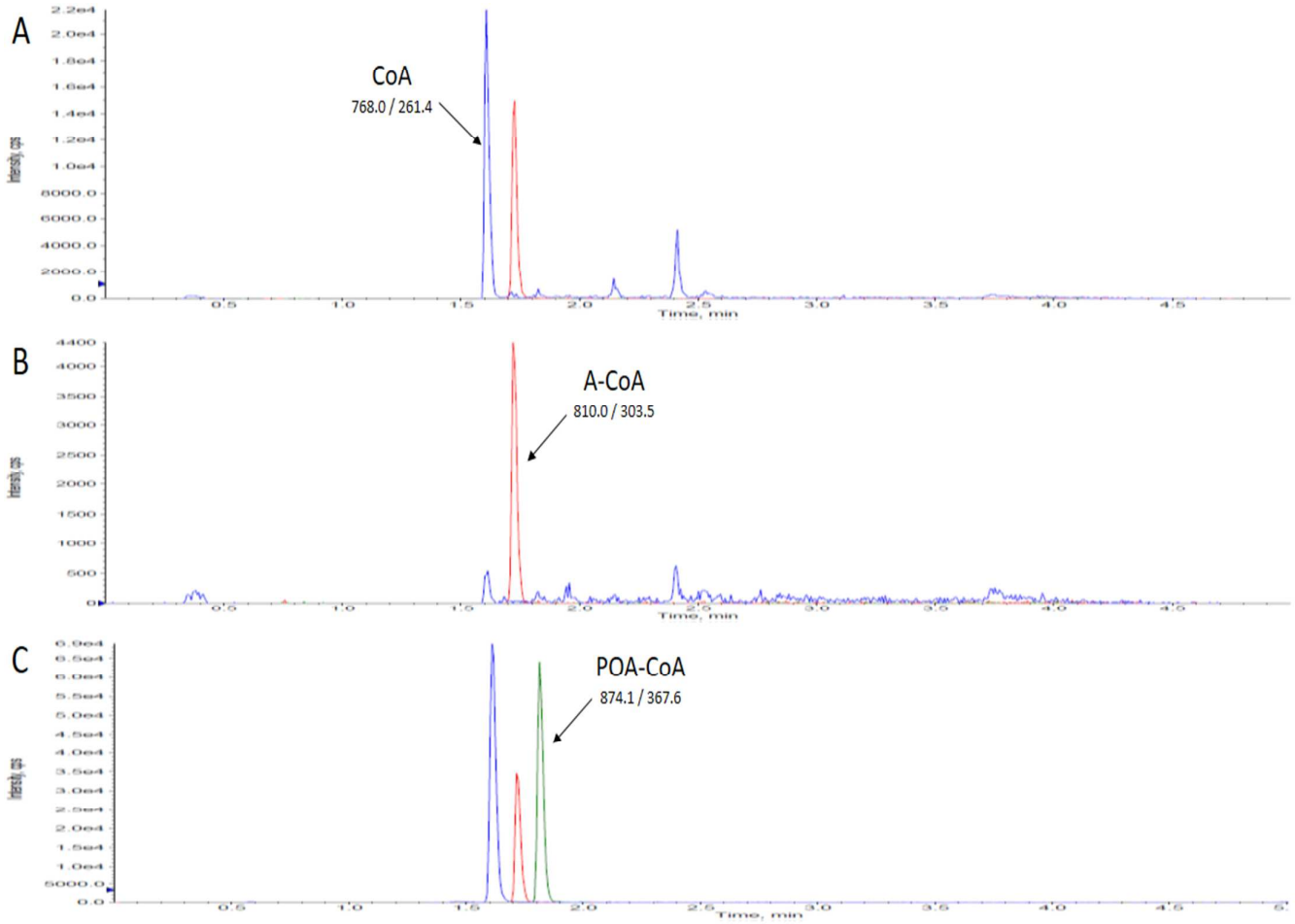

Figure S6. LC/MS/MS chromatograms displaying peaks (and mass transitions) for CoA, acetyl-CoA and POA-CoA. (A) CoA (blue) and acetyl-CoA (red) were detected in untreated lysate samples from *M. bovis* BCG. (B) 24 h after incubating BCG with POA, the concentrations of CoA and acetyl-CoA in lysate were markedly reduced. POA-CoA was not detected in BCG lysate either pre- or post- POA treatment. (C) POA-CoA (green peak) is clearly detected in *M. bovis* BCG 24 hours after lysate samples were spiked with the metabolite POA-CoA (0.5 μM). The recovery of POA-CoA in this sample is 104%.

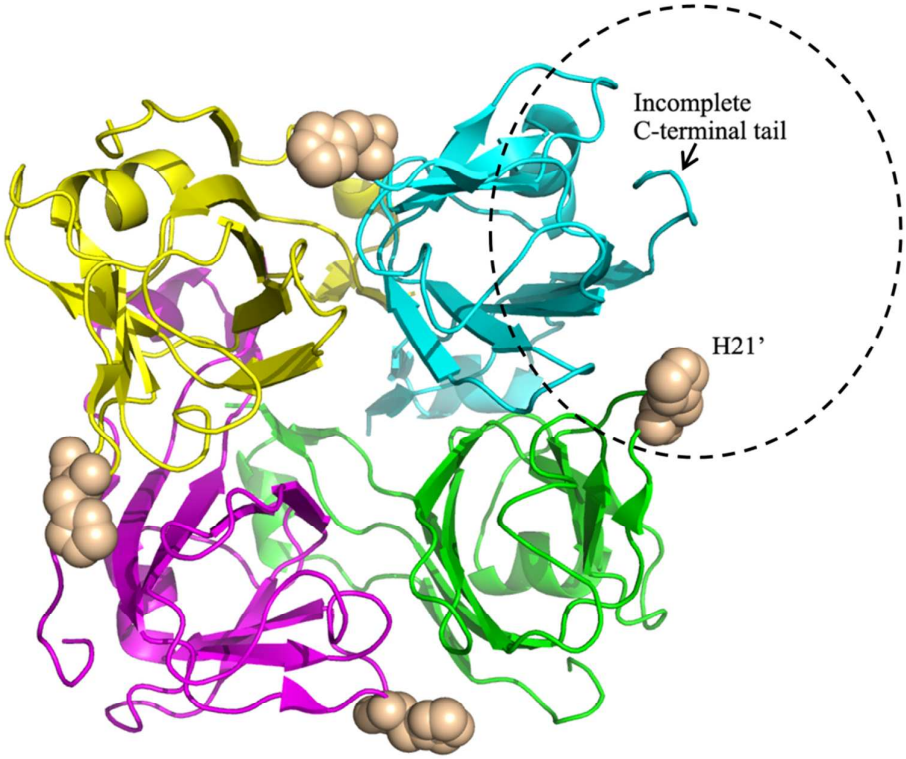

Figure S7. Structure of the PanD tetramer with the position of His21 indicated by spheres. The location of the incomplete C-terminal tail is shown. A circle is drawn to show that the C-terminal tail and the autocatalytic site may be in the same vicinity. The crystal structure of *M. tuberculosis* PanD (PDB ID: 2C45) is shown as reported in (*1*).

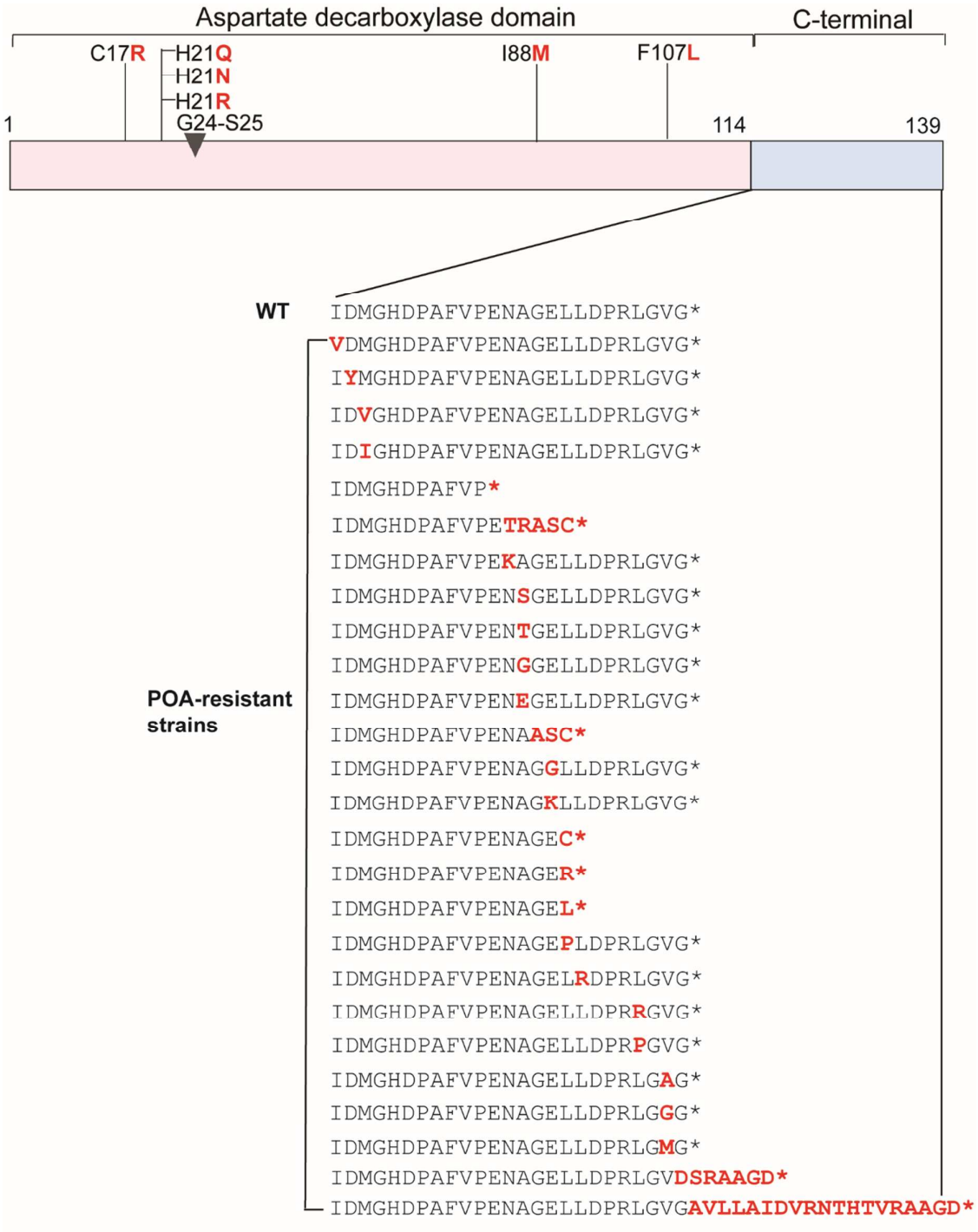

Figure S8. Mapping of POA-resistance mutations in aspartate decarboxylase PanD. Domain mapping according to (*1*). *panD* gene sequencing and mutation identification in POA-resistant *M. bovis* BCG isolated in (*2*) or POA-resistant *M. tuberculosis* H37Rv isolated and described in (*2-4*) was performed as detailed in (*4*). Altered amino acid residues within PanD in POA-resistant strains are indicated in bold red. The sequence of the C-terminal PanD wild-type protein are expanded below the schematic and aligned with sequences of the C-terminal of PanD found in different POA-resistant strains. * indicates Stop codon.

1. Gopalan, G., Chopra, S., Ranganathan, A., and Swaminathan, K. (2006) Crystal structure of uncleaved L-aspartate-α-decarboxylase from Mycobacterium tuberculosis. *Proteins 65*, 796-802. DOI: 10.1002/prot.21126.
2. Gopal, P., Yee, M., Sarathy, J., Low, J. L., Sarathy, J. P., Kaya, F., Dartois, V., Gengenbacher, M., and Dick, T. (2016) Pyrazinamide Resistance Is Caused by Two Distinct Mechanisms: Prevention of Coenzyme A Depletion and Loss of Virulence Factor Synthesis. *ACS Infect Dis 2*, 616-626. DOI: 10.1021/acsinfecdis.6b00070.
3. Yee, M., Gopal, P., and Dick, T. (2017) Missense Mutations in the Unfoldase ClpC1 of the Caseinolytic Protease Complex Are Associated with Pyrazinamide Resistance in Mycobacterium tuberculosis. *Antimicrob Ag Chemother 61*, e02342-02316. DOI: 10.1128/AAC.02342-16.
4. Gopal, P., Tasneen, R., Yee, M., Lanoix, J.-P., Sarathy, J., Rasic, G., Li, L., Dartois, V., Nuermberger, E., and Dick, T. (2017) In Vivo-Selected Pyrazinoic Acid-Resistant Mycobacterium tuberculosis Strains Harbor Missense Mutations in the Aspartate Decarboxylase PanD and the Unfoldase ClpC1. *ACS Infect Dis*. DOI: 10.1021/acsinfecdis.7b00017.

Supplemental methods

Sample Accessioning

Following receipt, samples were inventoried and immediately stored at -80^{o}C. Each sample received was accessioned into the Metabolon LIMS system and was assigned by the LIMS a unique identifier that was associated with the original source identifier only. This identifier was used to track all sample handling, tasks, results, etc. The samples (and all derived aliquots) were tracked by the LIMS system. All portions of any sample were automatically assigned their own unique identifiers by the LIMS when a new task was created; the relationship of these samples was also tracked. All samples were maintained at -80^{o}C until processed.

Sample Preparation

Samples were prepared using the automated MicroLab STAR® system from Hamilton Company. Several recovery standards were added prior to the first step in the extraction process for QC purposes. To remove protein, dissociate small molecules bound to protein or trapped in the precipitated protein matrix, and to recover chemically diverse metabolites, proteins were precipitated with methanol under vigorous shaking for 2 minutes (Glen Mills GenoGrinder 2000) followed by centrifugation. The resulting extract was divided into five fractions: two for analysis by two separate reverse phase (RP)/UPLC-MS/MS methods with positive ion mode electrospray ionization (ESI), one for analysis by RP/UPLC-MS/MS with negative ion

mode ESI, one for analysis by HILIC/UPLC-MS/MS with negative ion mode ESI, and one sample was reserved for backup. Samples were placed briefly on a TurboVap® (Zymark) to remove the organic solvent. The sample extracts were stored overnight under nitrogen before preparation for analysis.

QA/QC

Several types of controls were analyzed in concert with the experimental samples: a pooled matrix sample generated by taking a small volume of each experimental sample (or alternatively, use of a pool of well-characterized human plasma) served as a technical replicate throughout the data set; extracted water samples served as process blanks; and a cocktail of QC standards that were carefully chosen not to interfere with the measurement of endogenous compounds were spiked into every analyzed sample, allowed instrument performance monitoring and aided chromatographic alignment. Instrument variability was determined by calculating the median relative standard deviation (RSD) for the standards that were added to each sample prior to injection into the mass spectrometers. Overall process variability was determined by calculating the median RSD for all endogenous metabolites (i.e., non-instrument standards) present in 100% of the pooled matrix samples.

UPLC-MS/MS

All methods utilized a Waters ACQUITY ultra-performance liquid chromatography (UPLC) and a Thermo Scientific Q-Exactive high resolution/accurate mass spectrometer interfaced with a heated electrospray ionization (HESI-II) source and Orbitrap mass analyzer operated at 35,000 mass resolution. The sample extract was dried then reconstituted in solvents compatible to each of the four methods. Each reconstitution solvent contained a series of standards at fixed concentrations to ensure injection and chromatographic consistency. One aliquot was analyzed using acidic positive ion conditions, chromatographically optimized for more hydrophilic compounds (LC/MS Pos Early). In this method, the extract was gradient eluted from a C18 column (Waters UPLC BEH C18-2.1x100 mm, 1.7 µm) using water and methanol, containing 0.05% perfluoropentanoic acid (PFPA) and 0.1% formic acid (FA). Another aliquot was also analyzed using acidic positive ion conditions, however it was chromatographically optimized for more hydrophobic compounds (LC/MS Pos Late). In this method, the extract was gradient eluted from the same afore mentioned C18 column using methanol, acetonitrile, water, 0.05% PFPA and 0.01% FA and was operated at an overall higher organic content. Another aliquot was analyzed using basic negative ion optimized conditions using a separate dedicated C18 column (LC/MS Neg). The basic extracts were gradient eluted from the column

using methanol and water, however with 6.5mM Ammonium Bicarbonate at pH 8. The fourth aliquot was analyzed via negative ionization following elution from a HILIC column (Waters UPLC BEH Amide 2.1x150 mm, 1.7 µm) using a gradient consisting of water and acetonitrile with 10mM Ammonium Formate, pH 10.8 (LC/MS Polar). The MS analysis alternated between MS and data-dependent MS^n scans using dynamic exclusion. The scan range varied slighted between methods but covered 70-1000 m/z. Raw data files are archived and extracted as described below.

Bioinformatics

The informatics system consisted of four major components, the Laboratory Information Management System (LIMS), the data extraction and peak-identification software, data processing tools for QC and compound identification, and a collection of information interpretation and visualization tools for use by data analysts. The hardware and software foundations for these informatics components were the LAN backbone, and a database server running Oracle 10.2.0.1 Enterprise Edition.

LIMS

The purpose of the Metabolon LIMS system was to enable fully auditable laboratory automation through a secure, easy to use, and highly specialized system. The scope of the Metabolon LIMS system encompasses sample accessioning, sample preparation and instrumental analysis and reporting and advanced data analysis. All of the subsequent software systems are grounded in the LIMS data structures. It has been modified to leverage and interface with the in-house information extraction and data visualization systems, as well as third party instrumentation and data analysis software.

Data Extraction and Compound Identification

Raw data was extracted, peak-identified and QC processed using Metabolon's hardware and software. These systems are built on a web-service platform utilizing Microsoft's .NET technologies, which run on high-performance application servers and fiber-channel storage arrays in clusters to provide active failover and load-balancing. Compounds were identified by comparison to library entries of purified standards or recurrent unknown entities. Metabolon maintains a library based on authenticated standards that contains the retention time/index (RI), mass to charge ratio (*m/z)*, and chromatographic data (including MS/MS spectral data) on all molecules present in the library. Furthermore, biochemical identifications are based on three criteria: retention index within a narrow RI window of the proposed identification, accurate mass

match to the library +/- 10 ppm, and the MS/MS forward and reverse scores between the experimental data and authentic standards. The MS/MS scores are based on a comparison of the ions present in the experimental spectrum to the ions present in the library spectrum. While there may be similarities between these molecules based on one of these factors, the use of all three data points can be utilized to distinguish and differentiate biochemicals. More than 3300 commercially available purified standard compounds have been acquired and registered into LIMS for analysis on all platforms for determination of their analytical characteristics.

Curation

The QC and curation processes were designed to ensure accurate and consistent identification of true chemical entities, and to remove those representing system artefacts, mis-assignments, and background noise. Proprietary visualization and interpretation software were used by Metabolon to confirm the consistency of peak identification among the various samples. Library matches for each compound were checked for each sample and corrected if necessary.

Metabolite Quantification and Data Normalization

Peaks were quantified using area-under-the-curve. Essentially, each compound was corrected in run-day blocks by registering the medians to equal one (1.00) and normalizing each data point proportionately. In certain instances, biochemical data may have been normalized to an additional factor (e.g., cell counts, total protein as determined by Bradford assay, osmolality, etc.) to account for differences in metabolite levels due to differences in the amount of material present in each sample.

Detection of POA-CoA

POA-CoA was synthesized by Toronto Research Chemicals, Inc. (Toronto, ON) as a Coenzyme A S-Pyrazinecarboxylate Trisodium Salt (Molecular weight = 939.56). White to off-white solid; Purity: 96%. The reaction product was monitored by thin layer chromatography (TLC): C_{18}; Water: Methanol = 7: 3. The spots were visualized with UV and AMCS wherein a single spot was determined at R_f = 0.70. ^{1}H NMR (DMSO-d_6 + D_2O, D_2O), ^{31}P NMR (D_2O) and MS analysis confirmed that the compound conformed to structure. Elemental analysis found the composition of the compound to be: %C: 31.83, %H: 4.09, %N: 12.74 - consistent with the calculated values (%C: 33.24, %H: 3.75, %N: 13.42).

Mass analysis and detection were performed on an Applied Biosystems (Manchester, UK) 4000 Q-trap triple-quadrupole mass spectrometer equipped with a turbo ion-spray ionization source. The HPLC system is of the Agilent (Santa Clara, CA) 1260 series with a degasser, binary pump, autosampler and thermostated column compartment. The aqueous (A) and organic (B) mobile phases used were 5 mM ammonium acetate in water and 5 mM ammonium acetate in a water : acetonitrile mixture (1:19 v/v), respectively. Separation of all compounds was achieved by reverse phase chromatography using a Phenomenex Luna 3µ C18 (100 Å, 150 x 2 mm) column and the following gradient conditions: 0.0 min, 5% B; 3.0 min, 65% B; 3.01 min, 95% B; 4.0 min, 95% B; 4.01 min, 5% B; 5.5 min, 5% B. Calibration standards were prepared in the range of 5 to 10,000ng/ml. Quantification of POA-CoA and IS (Pyrazinamide-d3) was performed using multiple reaction monitoring (MRM) with the transitions 874.0→ 367.60 and 128.20→ 84.10, respectively. Data collection and processing were performed with Analyst 1.6.2 software.

TABLE S1. List of 343 detected metabolites and their fold change over untreated controls in POA-treated *M. bovis* BCG

Super Pathway	Sub Pathway	Biochemical Name	1mM POA/ Untreated 4h	ANOVA p-value	4mM POA/ Untreated 4h	ANOVA p-value	1mM POA/ Untreated 24h	ANOVA p-value	4mM POA/ Untreated 24h	ANOVA p-value
Amino Acid	Glycine, Serine and Threonine Metabolism	Glycine[1]	1.01	0.9116	1.14	0.1331	1.23	0.0167	1.2	0.0321
		Betaine[1]	1	0.9446	0.51	0.0004	1.07	0.7676	0.75	0.0295
		betaine aldehyde[1]	1.09	0.8262	0.98	0.9677	1.67	0.3798	2.19	0.101
		Serine[1]	0.97	0.7968	0.96	0.5546	1.16	0.1267	1	0.962
		N-acetylserine[1]	1.13	0.3746	1.29	0.1306	1.08	0.7629	0.82	0.2454
		3-phosphoserine[1]	1.15	0.5085	0.84	0.4786	1.66	0.0413	1.55	0.1081
		Threonine[1]	0.98	0.7208	0.82	0.0094	0.98	0.7828	0.77	0.0009
		N-acetylthreonine[3]	1.12	0.3526	0.74	0.0147	0.97	0.8304	0.84	0.1536
		allo-threonine[4]	1.04	0.6361	0.85	0.8551	0.93	0.7093	0.68	0.5628
		2-methylserine[1]	0.76	0.0083	0.63	4.24E-05	0.86	0.1122	0.49	5.49E-08
		O-acetylhomoserine[1]	1.01	0.9014	1.06	0.7289	0.8	0.0683	0.62	0.0007
		homoserine lactone[1]	1.29	0.1131	1.01	0.9498	1.57	0.0062	1.46	0.0154
	Alanine and Aspartate Metabolism	Alanine[1]	0.87	0.0659	0.89	0.0884	1.13	0.0912	1.03	0.7657
		Aspartate[1]	0.9	0.2609	0.8	0.0232	1.17	0.1024	0.96	0.4292
		Asparagine[1]	0.82	0.113	0.82	0.128	1.07	0.5661	0.86	0.1691
		cyano-alanine[4]	0.9	0.6618	0.32	1.49E-05	1.14	0.5354	0.4	0.0002
		3-sulfo-L-alanine[4]	0.89	0.1996	0.54	2.08E-06	1.06	0.6491	0.26	2.37E-13
	Glutamate Metabolism	Glutamate[1]	0.83	0.0111	0.71	4.45E-05	0.9	0.1686	0.58	2.49E-08
		Glutamine[1]	0.86	0.1156	0.74	0.0027	0.97	0.8566	0.74	0.0029
		N-acetylglutamate[4]	0.91	0.3765	0.75	0.0108	0.85	0.1354	0.41	2.10E-09
		N-acetylglutamine[4]	2.14	3.23E-05	6.43	1.58E-12	1.11	0.4191	1.87	0.0004
		gamma-aminobutyrate (GABA)[1]	0.82	0.042	0.97	0.644	0.59	7.51E-06	0.35	8.87E-12
		glutamate, gamma-methyl ester[1]	0.96	0.6364	0.78	0.0181	0.72	0.0023	0.45	1.98E-08
		Citramalate[4]	0.83	0.2145	0.66	0.0035	1.44	0.0117	0.71	0.0117
	Histidine Metabolism	Histidine[3]	0.87	0.1325	0.76	0.0051	1.32	0.0046	1.1	0.3407
		N-acetylhistidine[1]	1.43	0.0237	2.52	2.04E-06	0.93	0.6476	1.13	0.6245
	Lysine Metabolism	Lysine[1]	1.07	0.4924	1.1	0.3463	1.2	0.0523	1.24	0.0375
		N2-acetyllysine[3]	1.66	0.0032	1.88	0.0005	0.93	0.6368	1.2	0.3155

	N6-acetyllysine[4]	1.26	0.0922	1.23	0.113	0.87	0.2306	0.85	0.1915
	N6,N6,N6-trimethyllysine[1]	1.06	0.534	1.08	0.3691	1.25	0.012	1.05	0.6277
	2-aminoadipate[4]	1.16	0.1387	0.98	0.8085	1.03	0.7847	1.02	0.9374
	glutarate (pentanedioate)[4]	0.83	0.1299	0.87	0.2633	2.19	2.19E-07	1.57	0.0009
	Pipecolate[1]	1.14	0.3141	1.17	0.2133	0.92	0.4668	0.94	0.5357
Phenylalanine and Tyrosine Metabolism	Phenylalanine[1]	0.94	0.4808	0.84	0.0538	1.6	1.00E-05	1.37	0.0021
	Phenylpyruvate[4]	1.57	0.0086	1.48	0.0164	1.66	0.0016	1.44	0.0164
	phenyllactate (PLA)[4]	1.55	0.0003	1.57	0.0003	1.52	0.0005	2.57	1.74E-09
	Tyrosine[4]	1.08	0.4542	0.83	0.0554	2.13	5.95E-09	1.93	1.05E-07
	N-acetyltyrosine[3]	1.87	0.003	0.91	0.7619	2.24	0.0004	1.91	0.0093
	p-cresol sulfate[3]	1.14	0.0977	1.03	0.691	1.11	0.1459	0.94	0.4992
	O-methyltyrosine[1]	1.2	0.1688	1.19	0.27	1.54	0.0043	1.37	0.0362
Tryptophan Metabolism	Tryptophan[1]	0.96	0.563	0.94	0.4125	1.46	4.26E-05	1.47	4.94E-05
	Thioproline[1]	1.12	0.4385	0.82	0.1045	1.29	0.0534	0.72	0.0115
Leucine, Isoleucine and Valine Metabolism	Leucine[1]	0.86	0.1485	0.72	0.004	1.04	0.6603	0.88	0.1434
	isovaleryl/2-methylbutyryl CoA[4]	1.53	0.0018	1.71	0.0002	1.63	0.0004	2.01	6.74E-06
	Methylsuccinate[4]	0.93	0.4356	0.76	0.0064	0.88	0.2336	0.35	7.04E-11
	Isoleucine[1]	0.87	0.1312	0.75	0.0053	1.06	0.4598	0.89	0.1829
	butyryl/isobutyryl CoA[4]	1.15	0.3932	1.25	0.1981	0.61	0.0073	0.55	0.0021
	Ethylmalonate[4]	1.12	0.577	1.15	0.4152	0.48	0.0004	0.58	0.0029
	Valine[1]	0.82	0.0745	0.75	0.017	0.63	0.0005	0.46	2.10E-07
	N-acetylvaline[3]	0.83	0.3944	1.01	0.7549	0.7	0.0218	0.55	0.0013
	3-hydroxyisobutyrate[4]	1.19	0.3245	1.32	0.1631	0.79	0.1773	0.73	0.0671
Methionine, Cysteine, SAM and Taurine Metabolism	Methionine[1]	0.84	0.2116	0.52	3.49E-05	0.71	0.0179	0.49	7.74E-06
	N-acetylmethionine[4]	0.95	0.696	0.63	0.0027	0.65	0.0056	0.56	9.84E-05
	N-formylmethionine[3]	1.11	0.3223	1.34	0.0088	1.21	0.0894	1.42	0.004
	methionine sulfoxide[1]	0.85	0.1905	0.66	0.0022	0.8	0.0527	0.73	0.0194
	S-adenosylmethionine (SAM)[1]	1.02	0.844	0.84	0.0942	1.18	0.1656	1.27	0.04
	S-adenosylhomocysteine (SAH)[1]	1.01	0.8727	0.97	0.672	1.11	0.1399	1.14	0.106
	Cystathionine[1]	0.68	0.0071	0.53	5.08E-05	0.58	0.0004	0.6	0.0006
	Cysteine[1]	1.01	0.8332	0.8	0.0013	1.01	0.8739	0.66	6.00E-07
	S-methylcysteine[1]	1.25	0.1383	1.33	0.0755	0.85	0.2655	0.73	0.05
	cysteine sulfinic acid[1]	0.93	0.4775	0.83	0.0605	1.02	0.9175	0.59	1.10E-05
Urea cycle; Arginine and	Arginine[1]	1.04	0.665	0.97	0.7067	1.68	4.79E-05	1.68	6.92E-05

	Proline Metabolism	Ornithine[1]	1.03	0.8097	0.89	0.2937	1.34	0.0216	0.82	0.089
		Proline[1]	0.93	0.3591	0.9	0.172	1.09	0.25	1	0.9727
		Citrulline[1]	0.91	0.3275	0.83	0.0423	1.06	0.6054	0.64	2.82E-05
		Argininosuccinate[1]	1.01	0.8873	1.1	0.4625	1.06	0.6487	1.21	0.0987
		Homocitrulline[4]	1.12	0.3209	0.75	0.0189	1.06	0.5319	0.76	0.0244
		N-acetylarginine[1]	1.22	0.1877	2.3	5.14E-06	1.29	0.091	1.35	0.1011
		N-delta-acetylornithine[4]	1.13	0.5339	1.01	0.9846	1.17	0.4712	0.53	0.0005
		N-alpha-acetylornithine[4]	1.05	0.5879	0.97	0.7468	1.03	0.7646	0.5	1.87E-08
		trans-4-hydroxyproline[1]	1.12	0.3065	1.03	0.9609	1.56	0.0008	1.26	0.0626
	Polyamine Metabolism	5-methylthioadenosine (MTA)[1]	1.15	0.3638	0.98	0.7726	1.5	0.0057	1.42	0.0168
		4-acetamidobutanoate[4]	0.84	0.508	1.79	0.035	0.61	0.0253	0.52	0.0055
		gamma-glutamyl-GABA[1]	0.58	0.001	0.72	0.0192	0.23	1.38E-10	0.05	0.00E+00
	Guanidino and Acetamido Metabolism	4-guanidinobutanoate[1]	0.97	0.8767	1.12	0.5679	1.36	0.0966	1.36	0.2287
	Glutathione Metabolism	5-oxoproline[3]	1.02	0.812	0.93	0.3623	1.26	0.0091	0.99	0.8499
Peptide	Gamma-glutamyl Amino Acid	gamma-glutamylalanine[1]	0.57	0.0777	0.45	0.0122	0.52	0.0295	0.08	1.19E-09
		gamma-glutamylcysteine[1]	0.45	0.0219	0.21	5.64E-05	0.42	0.0073	0.11	1.23E-06
		gamma-glutamylglutamate[1]	0.56	1.63E-05	0.33	1.13E-10	0.52	2.98E-06	0.13	0.00E+00
		gamma-glutamylglutamine[1]	0.67	0.0979	0.47	0.0015	0.67	0.069	0.22	1.86E-07
		gamma-glutamylisoleucine[1]	0.72	0.0215	0.34	1.06E-08	0.47	5.12E-06	0.17	2.41E-13
		gamma-glutamylleucine[1]	0.62	0.0007	0.3	3.53E-10	0.31	7.53E-10	0.12	1.00E-15
		gamma-glutamyl-alpha-lysine[1]	0.81	0.1359	0.79	0.114	0.81	0.1928	0.6	0.0007
		gamma-glutamyl-epsilon-lysine[1]	0.96	0.527	0.89	0.133	1.01	0.8099	0.84	0.0215
		gamma-glutamylmethionine[1]	0.58	0.0094	0.3	1.59E-06	0.44	0.0001	0.12	1.73E-11
		gamma-glutamylphenylalanine[1]	0.72	0.0373	0.34	5.08E-08	1.11	0.6176	0.46	4.08E-06
		gamma-glutamylthreonine[1]	0.67	0.0805	0.37	6.13E-05	0.55	0.0036	0.08	1.37E-12
		gamma-glutamylvaline[1]	0.59	0.0005	0.32	7.83E-09	0.22	3.16E-11	0.04	0.00E+00
	Dipeptide	Glycylleucine[1]	0.89	0.4182	0.88	0.3429	1.83	0.0001	1.99	6.24E-05
		Glycylvaline[1]	0.85	0.2783	0.81	0.1606	1.79	0.0004	1.39	0.0997
		Phenylalanylglycine[1]	1.36	0.1801	1.6	0.0405	1.48	0.0995	1.65	0.0405
		Prolylglycine[1]	0.85	0.4576	0.73	0.1526	2.35	0.0006	1.67	0.1553
		Valylglutamine[1]	1.32	0.1512	1.64	0.0121	0.97	0.9679	0.85	0.3235
		Leucylglutamine[1]	1.21	0.2781	1.39	0.0705	1.18	0.3088	1.36	0.0919
Carbohydrate	Glycolysis,	Glucose[4]	1.24	0.0638	1.32	0.0182	1.56	0.0002	1.68	5.58E-05

	Gluconeogenesis, and Pyruvate Metabolism	glucose 6-phosphate[4]	1.19	0.3272	1.06	0.8352	1.21	0.4649	0.84	0.3089
		fructose-6-phosphate[4]	1.08	0.4578	0.99	0.8539	1.28	0.0112	0.85	0.086
		Isobar: fructose 1,6-diphosphate, glucose 1,6-diphosphate, myo-inositol 1,4 or 1,3-diphosphate[3]	1.27	0.198	1.24	0.4207	1.63	0.007	1.29	0.1525
		dihydroxyacetone phosphate (DHAP)[4]	1.4	0.0378	1.06	0.7261	1.47	0.0255	1.58	0.0092
		glyceraldehyde 3-phosphate[4]	1.25	0.3323	1.13	0.4339	1.28	0.6547	0.79	0.8014
		2-phosphoglycerate[4]	1.78	0.126	1.56	0.2409	3.59	0.0034	1.52	0.5099
		3-phosphoglycerate[3]	1.31	0.0962	1.38	0.0671	2.37	1.08E-05	2.5	4.77E-06
		phosphoenolpyruvate (PEP)[3]	1.15	0.4925	1.39	0.1222	2.16	0.0005	2.94	7.69E-06
		Pyruvate[4]	1.2	0.1606	1.23	0.1563	1.44	0.0111	1.43	0.0125
		Glycerate[4]	1.13	0.2779	1.28	0.0276	1.3	0.0167	1.49	0.0009
	Pentose Phosphate Pathway	6-phosphogluconate[3]	1.15	0.374	1.25	0.2314	1.83	0.0003	1.53	0.0074
		ribose 5-phosphate[4]	0.82	0.883	0.77	0.9823	1.6	0.241	1.23	0.484
		ribose 1-phosphate[4]	1.19	0.1797	1.18	0.2118	1.76	0.0001	1.58	0.0016
		5-phosphoribosyl diphosphate (PRPP)[3]	1.27	0.2754	1	0.9159	1.25	0.2846	0.89	0.9592
		sedoheptulose-7-phosphate[4]	1.03	0.7646	1.02	0.816	1.17	0.0725	0.92	0.2975
		ribulose/xylulose 5-phosphate[4]	1.14	0.3704	1.01	0.9934	1.4	0.0254	1.25	0.1608
	Pentose Metabolism	Ribose[4]	1.11	0.3388	1.19	0.0941	1.46	0.0004	1.62	3.12E-05
		Ribitol[4]	1.13	0.1971	1.17	0.0996	1.75	3.00E-06	2.56	2.44E-10
		Ribonate[4]	0.91	0.33	0.61	3.34E-05	1.33	0.008	0.77	0.0077
		fucose-1-phosphate[4]	1.27	0.1455	1.06	0.5205	1.34	0.1793	0.88	0.589
		adenosine-5'-diphosphoglucose[4]	1.26	0.124	1.21	0.1949	1.63	0.0014	1.6	0.0018
		arabitol/xylitol[4]	1.26	0.0122	1.47	0.0001	1.53	4.68E-05	1.92	8.22E-08
		ribulose/xylulose[4]	1.04	0.7431	1.05	0.6708	1.38	0.0066	1.41	0.0055
		arabonate/xylonate[4]	1.05	0.9152	0.97	0.8193	1.35	0.1419	0.85	0.3775
		Sedoheptulose[4]	1.16	0.1088	1.31	0.0051	1.76	7.10E-07	2.31	4.00E-10
	Glycogen Metabolism	Maltopentaose[4]	0.98	0.798	0.97	0.7486	1.55	0.0003	1.5	0.0008
		Maltotetraose[4]	0.98	0.7879	0.85	0.0245	1.16	0.04	0.77	0.0008
		Maltotriose[4]	0.95	0.6206	0.9	0.3318	1.49	0.0012	1.54	0.0005
		Maltose[4]	1.05	0.6871	1.13	0.2594	0.89	0.356	1.2	0.0846
	Disaccharides and Oligosaccharides	Trehalose[4]	1.22	0.011	1.41	6.66E-05	1.74	2.33E-08	2.08	9.34E-11
		trehalose 6-phosphate[3]	1.01	0.8479	0.98	0.7501	1.21	0.0172	1.22	0.0166
	Fructose, Mannose and	Fructose[4]	1.21	0.0132	1.31	0.0007	1.39	7.89E-05	1.76	2.18E-08

	Galactose Metabolism	mannitol/sorbitol[4]	1.11	0.1851	1.03	0.7115	1.44	4.53E-05	1.21	0.03
		Mannose[4]	0.96	0.7376	0.98	0.8668	1.15	0.1496	0.82	0.0463
		mannose-6-phosphate[4]	1.01	0.8726	0.93	0.3505	1.29	0.0067	0.9	0.2144
		Rhamnose[4]	0.69	0.2521	0.66	0.1357	0.7	0.263	0.69	0.2792
		galactitol (dulcitol)[4]	1.17	0.0451	0.99	0.8915	1.25	0.0045	0.78	0.0015
		galactose 1-phosphate[4]	1.16	0.1169	1.13	0.2041	1.66	3.78E-06	1.44	0.0004
		Galactonate[4]	0.9	0.5881	0.64	0.0116	0.87	0.5218	0.35	7.11E-07
	Nucleotide Sugar	UDP-glucose[4]	1.39	0.0572	1.28	0.1534	1.14	0.4336	0.83	0.3494
		UDP-galactose[4]	1.87	0.2015	2.08	0.1711	0.7	0.3408	0.41	0.1743
		UDP-N-acetylglucosamine/galactosamine[4]	1.11	0.4001	0.89	0.3237	0.86	0.1849	0.58	0.0002
	Aminosugar Metabolism	glucosamine-6-phosphate[4]	1.08	0.4612	1	0.8762	1.24	0.0814	0.89	0.2652
		Glucuronate[4]	1.12	0.5984	0.81	0.4021	1.03	0.6268	0.55	0.0211
		N-acetyl-glucosamine 1-phosphate[4]	1.03	0.7719	0.9	0.2851	1.2	0.0522	0.79	0.0136
		N-acetylmuramate[3]	1.17	0.3267	0.86	0.4998	1.01	0.8916	0.7	0.0309
		Erythronate[4]	1.15	0.0826	1.04	0.675	1.21	0.0148	1.02	0.8679
		N-acetylglucosamine/N-acetylgalactosamine[1]	0.83	0.1224	1	0.9807	1.38	0.0092	0.86	0.3428
Energy	TCA Cycle	Citrate[3]	1.12	0.5578	1.17	0.4196	1.02	0.9713	0.85	0.2896
		aconitate [cis or trans][4]	1.03	0.8562	1.35	0.1977	1.19	0.5548	0.96	0.7593
		Isocitrate[4]	1	0.9645	1.33	0.2691	1.27	0.4115	0.74	0.1772
		alpha-ketoglutarate[4]	0.94	0.523	0.9	0.2497	0.81	0.0289	0.52	1.28E-07
		Succinate[4]	1.05	0.4928	1.09	0.2372	1	0.9665	0.76	0.0004
		Fumarate[4]	1	0.9713	0.95	0.6788	0.75	0.0266	0.47	1.03E-06
		Malate[4]	1.08	0.4561	1.06	0.6646	1.1	0.4007	0.72	0.0072
		2-methylcitrate[3]	1.07	0.6145	1	0.9152	1.65	0.0001	1.36	0.0131
	Oxidative Phosphorylation	Acetylphosphate[4]	1.08	0.7604	1.15	0.539	1.27	0.2919	1.12	0.6043
		Phosphate[3]	1.06	0.4328	0.97	0.5732	1.29	0.0007	1.04	0.608
Lipid	Medium Chain Fatty Acid	caprylate (8:0)[3]	1.33	0.0524	1.37	0.0547	2.23	2.58E-06	2.96	1.82E-08
		caprate (10:0)[3]	1.16	0.222	1.16	0.2687	2.12	7.58E-06	3.1	7.30E-09
		laurate (12:0)[3]	0.95	0.743	0.87	0.3238	1.57	0.0013	1.84	5.31E-05
		5-dodecenoate (12:1n7)[3]	0.97	0.8432	0.66	0.1876	2.51	0.0035	2.14	0.0086
	Long Chain Fatty Acid	myristate (14:0)[3]	0.99	0.9896	0.88	0.2702	1.78	2.94E-05	2.14	5.05E-07
		pentadecanoate (15:0)[3]	1.05	0.5871	0.91	0.4344	1.37	0.0096	1.59	0.0005
		palmitate (16:0)[3]	0.98	0.9094	0.77	0.0595	1.21	0.1689	1.44	0.0146

	palmitelaidate (tr 16:1n7)[3]	0.94	0.804	0.75	0.1115	1.65	0.0123	1.8	0.0027
	margarate (17:0)[3]	0.97	0.9075	0.79	0.1342	1.37	0.0376	1.48	0.0146
	10-heptadecenoate (17:1n7)[3]	0.95	0.8243	0.74	0.1031	1.34	0.1077	1.59	0.018
	stearate (18:0)[3]	1.03	0.7386	0.88	0.3266	1.53	0.0015	2	5.71E-06
	nonadecanoate (19:0)[3]	0.96	0.9589	0.85	0.3945	2.06	8.83E-05	2.97	2.64E-07
	10-nonadecenoate (19:1n9)[3]	0.94	0.8218	0.8	0.3397	1.25	0.2227	1.85	0.0053
	arachidate (20:0)[3]	1.04	0.7301	0.89	0.5749	1.82	0.0019	3.23	7.01E-07
	eicosenoate (20:1)[3]	0.98	0.9816	0.85	0.332	1.67	0.0033	2.58	2.41E-06
	erucate (22:1n9)[3]	1.16	0.4472	1.26	0.3429	3.6	1.70E-06	6.3	4.15E-09
	myristelaidate (tr 14:1n5)[3]	0.88	0.6781	0.66	0.1391	2.43	0.0031	1.81	0.0235
	oleate/vaccenate (18:1)[3]	0.98	0.8902	0.82	0.0789	1.29	0.0325	1.47	0.002
Polyunsaturated Fatty Acid (n3 and n6)	linoelaidate (tr 18:2n6)[3]	0.92	0.691	0.74	0.1252	1.51	0.0518	1.78	0.0072
Fatty Acid, Branched	15-methylpalmitate[3]	0.95	0.6741	0.79	0.0502	1.31	0.0296	1.42	0.0087
	17-methylstearate[3]	0.93	0.7313	0.69	0.0324	1.17	0.2708	1.31	0.0927
Fatty Acid, Dicarboxylate	dimethylmalonic acid[4]	2.32	1.01E-05	1.86	0.0003	0.94	0.6664	0.46	5.46E-05
	2-hydroxyadipate[4]	0.93	0.9671	0.48	0.0651	1.86	0.0999	3.4	0.0716
	pimelate (heptanedioate)[4]	1.39	0.0006	1.85	8.50E-08	2.12	1.22E-09	2.22	4.42E-10
	suberate (octanedioate)[4]	1.14	0.3706	1.75	0.0007	1.44	0.0071	1.89	9.06E-05
	azelate (nonanedioate)[4]	1.27	0.0673	2.66	2.06E-08	1.33	0.0109	2.27	2.18E-07
	sebacate (decanedioate)[4]	1.32	0.007	2.08	4.48E-08	1.21	0.0464	1.91	5.84E-07
	Dodecanedioate[3]	1.12	0.755	1.34	0.1611	2.29	0.0002	4.16	1.64E-07
	Hexadecanedioate[3]	0.99	0.9551	1.49	0.3425	2.41	0.0161	3.31	0.003
Fatty Acid Synthesis	Malonate[4]	1.09	0.5327	1.04	0.8111	0.68	0.0027	0.64	0.001
Fatty Acid Metabolism	acetyl CoA[4]	1.05	0.746	1.07	0.6808	0.84	0.1816	0.96	0.6314
	hexanoyl CoA[3]	1.01	0.9938	1.22	0.3799	0.75	0.2028	0.68	0.1007
	decanoyl CoA[3]	0.75	0.4058	1.09	0.8576	0.62	0.0898	0.67	0.1822
Fatty Acid Metabolism(Acyl Carnitine)	Acetylcarnitine[1]	0.87	0.4355	0.7	0.047	1.17	0.427	1	0.8409
Ketone Bodies	3-hydroxybutyrate (BHBA)[4]	0.71	0.1049	1.4	0.2513	0.63	0.0495	1.3	0.37
Fatty Acid, Monohydroxy	4-hydroxybutyrate (GHB)[4]	0.92	0.4939	1.41	0.0233	0.57	0.0007	0.3	4.85E-09
	3-hydroxyoctanoate[3]	0.96	0.9297	1.22	0.3317	1.35	0.2287	1.53	0.2154
	3-hydroxydecanoate[3]	1.15	0.1929	1.39	0.0079	1.72	0.0001	1.89	1.26E-05
	3-hydroxylaurate[3]	1.16	0.4129	0.87	0.5973	1.07	0.7957	1.23	0.2174
	3-hydroxypalmitate[3]	1.07	0.4842	1.11	0.4347	1.51	0.0017	1.58	0.0008

	13-HODE + 9-HODE[3]	0.85	0.1424	0.98	0.9889	1.3	0.1624	1.34	0.1307
	3-hydroxystearate[3]	1.17	0.4548	1.28	0.2407	1.67	0.007	1.95	0.0021
Inositol Metabolism	myo-inositol[4]	1.29	0.0634	1.53	0.002	2.05	4.88E-06	2.24	1.51E-06
	epi-inositol[4]	1.14	0.1688	1.14	0.1762	1.35	0.0025	1.07	0.6496
	inositol 1-phosphate (I1P)[4]	2.08	0.2907	1.81	0.345	1.72	0.0831	1.47	0.3303
Phospholipid Metabolism	Choline[1]	0.99	0.9421	1.21	0.1116	1.21	0.067	1.35	0.0065
	choline phosphate[1]	1.15	0.5229	1.08	0.6145	1.09	0.7349	0.9	0.4141
	glycerophosphorylcholine (GPC)[1]	0.84	0.2263	0.94	0.4834	1.09	0.5412	1.09	0.5089
	Glycerophosphoethanolamine[4]	0.99	0.8901	0.99	0.8729	0.99	0.9951	0.95	0.5357
	Glycerophosphoinositol[3]	0.91	0.1675	0.88	0.0699	1.15	0.045	0.92	0.224
	1,2-dipalmitoyl-GPC (16:0/16:0)[2]	1.19	0.7458	0.95	0.6513	1.19	0.9556	1.14	0.6958
	1,2-dipalmitoyl-GPE (16:0/16:0)[2]	1.1	0.5083	1.01	0.9493	1.19	0.129	1.35	0.0265
	1-palmitoyl-2-oleoyl-GPA[2] (16:0/18:1)	0.95	0.5418	0.82	0.03	1.03	0.7649	0.84	0.042
	1-palmitoyl-2-oleoyl-GPC (16:0/18:1)[2]	1	0.953	0.99	0.8681	1.32	0.0193	1.18	0.1589
	1-stearoyl-2-oleoyl-GPC (18:0/18:1)[2]	0.96	0.7007	1.01	0.9596	1.36	0.0281	1.24	0.101
	1-stearoyl-2-oleoyl-GPI (18:0/18:1)2	1.02	0.8225	0.93	0.4638	1.78	1.80E-05	1.44	0.0029
	1-oleoyl-2-linoleoyl-GPC (18:1/18:2)[2]	0.83	0.5232	0.83	0.5169	1.06	0.956	0.97	0.8096
	1-palmitoyl-2-oleoyl-GPG (16:0/18:1)[2]	1.02	0.8595	1.02	0.9723	1.26	0.055	1.4	0.0123
	1-palmitoyl-2-oleoyl-GPE (16:0/18:1)[2]	0.98	0.7626	0.93	0.2726	1.05	0.4227	0.96	0.438
	1-stearoyl-2-oleoyl-GPE (18:0/18:1)[2]	1	0.9864	0.95	0.5277	1.49	6.54E-05	1.42	0.0005
	1,2-dioleoyl-GPE (18:1/18:1)[2]	1.01	0.9292	0.98	0.864	1.47	0.0256	1.42	0.031
	1-palmitoyl-2-oleoyl-GPI (16:0/18:1)[2]	1	0.9866	0.98	0.7412	1.18	0.0045	1.03	0.5835
	1-stearoyl-2-oleoyl-GPG (18:0/18:1)[2]	1.02	0.8804	0.93	0.539	1.77	0.0002	1.77	0.0004
	1-oleoyl-2-linoleoyl-GPE (18:1/18:2)[2]	0.97	0.8495	1.03	0.8447	1.69	0.004	1.88	0.0007
	1,2-dipalmitoyl-GPG (16:0/16:0)[4]	1.09	0.8162	1.07	0.7423	1.09	0.5117	1.37	0.2113
Lysolipid	1-palmitoyl-GPE (16:0)[3]	1.12	0.5139	0.88	0.5231	0.98	0.9345	1.29	0.2597
	1-stearoyl-GPE (18:0)[2]	1	0.9717	1.01	0.8292	1.11	0.3612	1.28	0.067
	2-stearoyl-GPE (18:0)[3]	1.25	0.4189	1	0.9663	1.4	0.1715	2.08	0.021
	1-oleoyl-GPE (18:1)[3]	1.16	0.4085	1.07	0.8072	1.12	0.4514	1.58	0.0371
	1-palmitoyl-GPI (16:0)[3]	0.97	0.9182	0.96	0.9008	1.37	0.0969	1.32	0.1509

		1-stearoyl-GPI (18:0)[3]	0.9	0.885	0.87	0.6641	1.86	0.0083	1.77	0.0168
		1-oleoyl-GPI (18:1)[3]	0.9	0.7611	0.97	0.9082	1.1	0.6141	1.18	0.6407
		1-palmitoyl-GPA (16:0)[3]	1.3	0.6625	1.07	0.9037	1.35	0.3397	1.66	0.2189
		1-stearoyl-GPA (18:0)[3]	0.92	0.889	0.92	0.889	5.58	0.0314	11.48	0.0105
		1-oleoyl-GPA (18:1)[3]	1.31	0.5019	0.82	0.7564	2.28	0.0688	1.97	0.2452
		1-palmitoyl-GPG (16:0)[2]	1.05	0.5229	0.99	0.7214	1.54	0.1057	1.47	0.1158
		1-oleoyl-GPG (18:1)[4]	1.55	0.1296	0.85	0.6015	2.18	0.0076	3.05	0.0012
		1-palmitoleoyl-2-oleoyl-GPA (16:1/18:1)[2]	1.28	0.414	0.95	0.6822	1.37	0.22	0.72	0.1163
	Glycerolipid Metabolism	Glycerol[3]	1.1	0.3671	1	0.985	1.24	0.0413	1.08	0.5309
		glycerol 3-phosphate[3]	1.12	0.097	1.03	0.6881	1.35	7.69E-05	1.25	0.0023
		Glycerophosphoglycerol[4]	1.15	0.4136	1.18	0.3353	1.73	0.003	1.78	0.0041
	Diacylglycerol	diacylglycerol (14:0/18:1, 16:0/16:1) [2][2]	0.98	0.953	0.75	0.1717	2.02	0.0152	1.52	0.0875
		oleoyl-linoleoyl-glycerol (18:1/18:2) [1][2]	1.1	0.7718	1.2	0.5441	2.54	0.0048	2.52	0.0048
		oleoyl-linoleoyl-glycerol (18:1/18:2) [2][2]	1.11	0.7976	1.24	0.5907	3.28	0.0023	3.73	0.0005
		palmitoyl-oleoyl-glycerol (16:0/18:1) [1][2]	1.02	0.8599	0.84	0.4517	2.03	0.0046	1.48	0.0597
		palmitoyl-oleoyl-glycerol (16:0/18:1) [2][2]	0.92	0.5892	0.75	0.092	1.24	0.3741	0.93	0.604
		palmitoyl-palmitoyl-glycerol (16:0/16:0) [2][2]	1.01	0.9888	1	1	2.66	0.2624	1.8	0.244
		oleoyl-oleoyl-glycerol (18:1/18:1) [1][2]	1.03	0.9257	1.06	0.8326	2.34	0.0167	2.1	0.0244
		oleoyl-oleoyl-glycerol (18:1/18:1) [2][2]	1.06	0.9233	1.1	0.8135	2.52	0.006	2.68	0.0021
	Sphingolipid Metabolism	Sphinganine[2]	0.99	0.9961	1.13	0.6274	1.46	0.2293	1.44	0.2822
		palmitoyl sphingomyelin (d18:1/16:0)[2]	1.05	0.7161	1.09	0.4943	1.33	0.0155	1.33	0.015
		stearoyl sphingomyelin (d18:1/18:0)[2]	1.13	0.9063	1.12	0.6158	1.15	0.968	1.63	0.1026
		sphingomyelin (d18:1/14:0, d16:1/16:0)[2]	1.08	0.533	1.04	0.8657	1.42	0.0118	1.34	0.0337
		sphingomyelin (d18:1/15:0, d16:1/17:0)[2]	1.01	0.9388	1.09	0.595	1.4	0.0281	1.37	0.0254
		sphingomyelin (d18:2/16:0, d18:1/16:1)[2]	1.03	0.8477	1.06	0.6686	1.19	0.3144	1.2	0.1955
		Sphingosine[2]	0.96	0.6698	1	0.9522	1.11	0.3168	1.55	0.0007
	Mevalonate Metabolism	3-hydroxy-3-methylglutarate[4]	1.43	0.0843	0.83	0.3154	0.96	0.9391	0.37	1.35E-05
	Sterol	4-cholesten-3-one[2]	1.07	0.7386	1.2	0.3696	1.1	0.6973	1.61	0.0723
Nucleotide	Purine Metabolism, (Hypo)Xanthine/Inosine containing	inosine 5'-monophosphate (IMP)[1]	1.03	0.7432	0.76	0.0056	1.21	0.0358	1.05	0.5836
		Inosine[4]	0.97	0.7554	1.18	0.0934	1.19	0.0669	1.43	0.0011

		Hypoxanthine[3]	0.94	0.6629	1.02	0.8373	1.05	0.759	1.1	0.4371
		Xanthine[4]	1.4	0.212	1.18	0.5631	1.46	0.3594	1.14	0.662
		Xanthosine[3]	0.89	0.5971	0.76	0.2458	0.65	0.0851	0.81	0.4646
		2'-deoxyinosine[3]	1.09	0.5416	1.51	0.0318	0.89	0.6806	1.25	0.1788
		Allantoin[3]	1.19	0.4704	1.08	0.8922	1.59	0.0248	1.19	0.4525
	Purine Metabolism, Adenine containing	adenosine 5'-diphosphate (ADP)[4]	1.16	0.3337	0.99	0.8967	1.81	0.0004	1.14	0.338
		adenosine 5'-monophosphate (AMP)[4]	1.05	0.3973	0.98	0.731	1.14	0.0379	0.99	0.7965
		adenosine 3'-monophosphate (3'-AMP)[4]	1.05	0.6203	0.97	0.744	1.14	0.1878	0.72	0.0006
		adenosine 3',5'-cyclic monophosphate (cAMP)[4]	1.26	0.256	1.09	0.6301	1.17	0.3394	1.69	0.0336
		adenosine 3',5'-diphosphate[3]	0.86	0.5548	1.35	0.2977	2.04	0.0065	1.89	0.0289
		Adenylosuccinate[3]	0.9	0.5382	0.94	0.6036	0.56	0.1321	0.31	0.0004
		Adenosine[1]	0.96	0.5632	0.94	0.4016	1.12	0.1319	0.98	0.7123
		Adenine[1]	0.96	0.6249	1.01	0.9914	1.23	0.0258	1	0.8891
		N6-methyladenosine[1]	0.88	0.4474	1.14	0.4922	0.85	0.2407	0.62	0.0084
		N6,N6-dimethyladenosine[1]	0.92	0.3768	0.96	0.6444	1.13	0.1791	0.99	0.825
		2'-deoxyadenosine 5'-monophosphate[4]	1	0.9807	0.9	0.2205	0.75	0.0036	0.48	6.63E-09
		2'-deoxyadenosine[1]	0.94	0.6413	0.96	0.7549	0.8	0.0777	0.53	1.45E-05
		N6-succinyladenosine[3]	1.04	0.7696	1.31	0.2349	0.81	0.4096	0.72	0.1742
	Purine Metabolism, Guanine containing	guanosine 5'- monophosphate (5'-GMP)[1]	0.97	0.6435	0.85	0.0252	1.03	0.7748	0.7	1.53E-05
		Guanosine[1]	0.94	0.5655	1	0.9872	1.23	0.0493	0.96	0.6475
		Guanine[3]	0.91	0.5732	0.86	0.3314	1	0.9942	0.57	0.0002
		2'-deoxyguanosine 5'-monophosphate (dGMP)[4]	1.04	0.7492	0.99	0.8372	0.87	0.2461	0.54	5.71E-06
		2'-deoxyguanosine[3]	1.08	0.6446	1.38	0.1124	0.92	0.912	0.81	0.4057
	Pyrimidine Metabolism, Orotate containing	N-carbamoylaspartate[4]	0.93	0.6993	0.59	0.0054	0.98	0.9572	0.72	0.0514
		Dihydroorotate[4]	0.69	0.0222	0.38	1.28E-06	0.95	0.7059	0.74	0.0366
		Orotate[4]	0.84	0.3729	0.62	0.0132	0.89	0.5273	0.59	0.0066
		Orotidine[4]	1.1	0.4395	0.76	0.0166	0.91	0.4364	0.44	1.58E-08
	Pyrimidine Metabolism, Uracil containing	uridine 5'-triphosphate (UTP)[3]	1.46	0.1253	1.21	0.57	2.15	0.0031	1.7	0.0244
		uridine 5'-diphosphate (UDP)[3]	1.21	0.1196	1.02	0.9118	1.66	0.0003	1.36	0.0198
		uridine 5'-monophosphate (UMP)[3]	1.03	0.722	1	0.9601	1.16	0.054	1	0.8862
		Uridine[4]	1.16	0.1345	1.37	0.0032	1.47	0.0004	1.38	0.0028
		Uracil[4]	1.18	0.2412	1.48	0.0114	1.5	0.0156	1.34	0.0683

		Pseudouridine[3]	0.92	0.5444	1.13	0.4998	0.82	0.2001	0.88	0.4806
		2'-deoxyuridine[3]	0.76	0.5809	1.22	0.4261	0.73	0.5965	0.72	0.3285
		beta-alanine[1]	0.08	8.57E-12	0.06	4.71E-13	0.04	3.00E-14	0.02	0.00E+00
	Pyrimidine Metabolism, Cytidine containing	cytidine triphosphate[3]	2	0.0372	2.27	0.0385	6.18	1.82E-05	4.5	0.0002
		cytidine diphosphate[3]	1.51	0.0578	1.51	0.1005	2.56	0.0002	2.33	0.0008
		cytidine 5'-monophosphate (5'-CMP)[4]	1.11	0.2085	1.13	0.1412	1.33	0.0011	1.15	0.1529
		Cytidine[3]	0.98	0.9857	1.26	0.1795	0.87	0.4372	0.89	0.503
		Cytosine[1]	1.2	0.1256	1.11	0.3616	1.03	0.8252	1.13	0.4199
		2'-deoxycytidine 5'-monophosphate[4]	1.04	0.6539	1.1	0.3087	0.89	0.1891	0.66	2.64E-05
		2'-deoxycytidine[1]	1.03	0.8262	1.36	0.0184	0.73	0.0103	0.61	0.0003
	Pyrimidine Metabolism, Thymine containing	thymidine 5'-monophosphate[4]	1.14	0.1975	1.04	0.7377	1.1	0.2599	0.9	0.2494
		thymidine 5'-diphosphate[4]	1.2	0.2115	1.18	0.2464	1.5	0.008	1.09	0.608
		Thymidine[4]	1.21	0.1809	1.23	0.1418	1.29	0.0682	1.15	0.2971
		Thymine[3]	1	0.9722	1.19	0.3011	0.95	0.5224	0.87	0.4061
	Purine and Pyrimidine Metabolism	Methylphosphate[4]	1.56	0.0086	1.24	0.1948	0.7	0.0227	0.85	0.1588
Cofactors and Vitamins	Nicotinate and Nicotinamide Metabolism	Nicotinate[1]	0.9	0.499	0.76	0.0733	2.23	5.19E-06	1.66	0.0042
		nicotinate ribonucleoside[1]	1.18	0.133	1.08	0.5273	1.71	6.50E-05	1.52	0.0015
		nicotinic acid mononucleotide (NaMN)[4]	1.11	0.2729	0.79	0.0158	1.5	0.0002	0.97	0.4949
		Nicotinamide[1]	1.05	0.6078	1.06	0.6186	1.2	0.1525	1.01	0.9836
		nicotinamide ribonucleotide (NMN)[1]	1.06	0.6556	1.16	0.2694	1.35	0.0294	1.37	0.058
		nicotinamide riboside[1]	1	0.9811	1.31	0.0307	1.48	0.0026	1.57	0.0012
		nicotinamide adenine dinucleotide (NAD+)[4]	1.11	0.1339	1.13	0.0945	1.37	8.38E-05	1.23	0.0077
		nicotinamide adenine dinucleotide reduced (NADH)[4]	0.8	0.4003	0.88	0.8371	2.37	0.0213	0.53	0.026
		adenosine 5'-diphosphoribose (ADP-ribose)[3]	0.99	0.9949	1.09	0.9788	0.84	0.4624	0.53	0.0246
	Riboflavin Metabolism	flavin adenine dinucleotide (FAD)[4]	1.12	0.2286	1.02	0.8272	1.18	0.0784	0.88	0.1531
		flavin mononucleotide (FMN)[3]	1.07	0.6688	1.09	0.8003	1.29	0.0865	0.98	0.8835
	Pantothenate and CoA Metabolism	Pantothenate[3]	0.3	1.21E-08	0.2	1.56E-11	0.18	4.89E-12	0.1	2.00E-15
		Phosphopantetheine[4]	0.95	0.7482	0.7	0.0276	0.28	6.39E-09	0.22	2.86E-10
		3'-dephosphocoenzyme A[4]	0.89	0.2417	0.8	0.0327	0.54	1.48E-06	0.42	2.77E-09
		3'-dephospho-acetyl-coenzyme A[3]	0.74	0.0871	0.86	0.4414	0.61	0.0094	0.7	0.0585
		coenzyme A[4]	0.97	0.8424	0.84	0.2877	0.51	0.0004	0.35	3.95E-07

	Ascorbate and Aldarate Metabolism	Threonate[4]	1.47	0.1043	1.66	0.0436	2.26	0.0133	1.84	0.0549
		Gulonate[4]	0.94	0.4806	0.49	1.56E-09	1.41	0.0003	0.82	0.02
	Biotin Metabolism	Biotin[1]	1.11	0.1774	1.16	0.0711	1.13	0.1062	1.02	0.8625
	Thiamine Metabolism	thiamin monophosphate[1]	0.9	0.2954	0.88	0.221	1.23	0.052	0.76	0.0074
		thiamin diphosphate[3]	1.22	0.3598	1.09	0.7819	1.21	0.3029	0.85	0.5195
		5-(2-Hydroxyethyl)-4-methylthiazole[1]	1.02	0.8857	0.89	0.5816	0.89	0.5242	1.17	0.3674
	Vitamin B6 Metabolism	pyridoxine (Vitamin B6)[1]	1.05	0.4986	0.95	0.4533	1.21	0.0068	1.09	0.2615
		Pyridoxamine[1]	0.8	0.1668	0.88	0.3909	0.95	0.914	0.77	0.1451
		pyridoxamine phosphate[1]	1.15	0.4685	1.3	0.2162	1.13	0.6695	0.98	0.9364
		pyridoxal phosphate[1]	1.2	0.1307	1.08	0.5537	1.33	0.0382	1.06	0.64
		Pyridoxal[1]	1.02	0.9076	0.98	0.7775	1.39	0.0007	0.99	0.8602
		Pyridoxate[4]	1.09	0.5151	0.91	0.461	1.13	0.316	0.94	0.4977
Xenobiotics	Benzoate Metabolism	Benzoate[3]	1.6	0.3317	2.11	0.0827	3.09	0.0189	2.34	0.1189
		4-hydroxybenzoate[4]	1.18	0.0687	1.33	0.003	1.11	0.1799	1.21	0.0271
	Food Component/Plant	Shikimate[4]	1.09	0.4038	1.12	0.2811	0.7	0.0021	0.63	0.0001
		Diaminopimelate[1]	0.89	0.2673	1.09	0.4803	0.82	0.0803	0.53	1.16E-06
		2,3-dihydroxyisovalerate[4]	1.19	0.4447	1.13	0.736	0.88	0.5208	0.44	0.0011
		2-isopropylmalate[4]	1.01	0.9936	0.94	0.643	0.66	0.0031	0.52	2.64E-05
		Gluconate[4]	1	0.9772	0.7	0.0034	1.04	0.6638	0.71	0.0051
		Ergothioneine[1]	0.96	0.5898	0.89	0.0865	1	0.9333	0.64	1.90E-07
		Erythritol[4]	1.05	0.611	1.1	0.293	1.05	0.5254	1.14	0.1635
		Histidinol[1]	0.84	0.3091	0.72	0.0308	0.65	0.0047	0.53	6.92E-05
		Quinate[4]	0.95	0.5112	0.35	1.51E-13	1.04	0.6627	0.37	3.24E-13
	Bacterial/Fungal	3-deoxyoctulosonate[4]	1.15	0.1125	0.98	0.791	1.56	1.72E-05	1.14	0.1684
	Chemical	Sulfate[3]	1.05	0.5041	0.96	0.4809	1.22	0.0062	1.02	0.8165
		glycerol 2-phosphate[4]	0.99	0.9364	0.74	0.0045	0.95	0.6049	0.59	9.70E-06
		Succinimide[4]	0.81	0.0811	1.02	0.9113	0.58	0.0001	0.32	4.10E-10

Green: indicates significant difference (p-value ≤ 0.05) between the groups shown, metabolite ratio of < 1.00
Light Green: narrowly missed statistical cutoff for significance 0.05 < p-value < 0.10, metabolite ratio of < 1.00
Red: indicates significant difference (p-value ≤ 0.05) between the groups shown; metabolite ratio of ≥ 1.00
Light Red: narrowly missed statistical cutoff for significance 0.05 < p-value < 0.10, metabolite ratio of ≥ 1.00
Black text and white cell: mean values are not significantly different for that comparison

[1] Metabolite identified by LC/MS Pos Early; [2] Metabolite identified by LC/MS Pos Late; [3] Metabolite identified by LC/MS Neg; [4] Metabolite identified by LC/MS Polar

TABLE S2. Data collection and scattering derived parameters for PanD proteins

Data collection parameters			
Instrument (source & detector)	Bruker NanoStar equipped with MetalJet eXcillum X-ray source and VÅNTEC-2000 detector		
Beam geometry	100 μm slit		
Wavelength (Å)	1.34		
q range (Å^{-1})	0.016 – 0.4		
Exposure time (min)	30 (6 frames x 5 min)		
Protein sample	**PanD$_{WT}$**	**PanD$_{H21R}$**	**PanD$_{127TRASC131}$**
Concentration range (mg mL^{-1})	1.5 – 7.4	5.0	6.5
Temperature (K)	288.15	288.15	288.15
Structural parameters†			
I(0) (arbitrary units) [from P(r)]	130.8 ± 0.40	129.9 ± 0.59	134.2 ± 0.65
R_g (Å) [from P(r)]	35.69 ± 0.12	35.56 ± 0.17	36.08 ± 0.16
I(0) (arbitrary units) (from Guinier)	131.7 ± 0.63	131.0 ± 0.82	135.3 ± 1.24
R_g (Å) (from Guinier)	35.40 ± 0.24	35.31 ± 0.31	35.46 ± 0.40
D_{max} (Å)	115.7 ± 10	115.9 ± 10	115.9 ± 10
Porod volume estimate (V_p) (Å^3)	~166702	~164000	~157000
DAMMIN excluded volume (V_{ex}) (Å^3)	~208100	~196200	~198600
Dry volume from sequence (Å^3) ‡	~18010	~18033	~17073
Molecular mass determination†			
Calculated monomeric *MM* (kDa) [from sequence*]	~14.9	~14.9	~14.1
MM from *Porod invariant* (V_p/1.6) (kDa)	104 ± 10	102 ± 10	98 ± 10
MM from *excluded volume* (V_{ex}/2) (kDa)	104 ± 10	97 ± 10	99 ± 10
MM from *volume of correlation* (V_c) (kDa)	103 ± 10	105 ± 10	101 ± 10
Software employed			
Primary data reduction	BRUKER SAS		

Data processing	PRIMUS
Ab initio analysis	DAMMIN
Validation and averaging	DAMAVER
Computation of model intensities	CRYSOL
Quaternary structure modeling	SASREF
3D graphics representations	PyMOL

* http://web.expasy.org/compute_pi/
‡ http://www.basic.northwestern.edu/biotools/proteincalc.html
†Reported for highest concentration data