Supplemental File 1:
Table 1. Full version of Table 2 showing comprehensive list of model modifications

	No.	Model Modification	Improvement on Yeast 7.11	Reference
Addition of Reactions to Yeast 7.11	1	Addition of alpha-keto isovalerate transport 3-methyl 2-oxobutanoate [m] ⇔ 3-methyl 2-oxobutanoate [**c**]	• *BAT1* reconciled from ESG to GG • *BAT1-BAT2* reconciled from SL2ES to SL2SL2.	[1] [2]
	2	Addition of pretyrosine formation prephenate [c] + L-glutamate [c] ⇔ 2-oxoglutarate [c] + pretyrosine [c] GPR: *YGL202W and YHR137W*	Addition of prephenate aminotransferase in the pretyrosine pathway and also retains *YGL202W* and *YHR137W* as GG.	[3] [4] [5]
	3	Addition of pretyrosine dehydratase pretyrosine [c] ⇔ CO_2 [c] + H_2O [c] + L-phenylalanine [c] GPR: *YNL316C*	Addition of pretyrosine dehydratase in the pretyrosine pathway also retaining *YNL316C* as GG.	[6]
	4	Addition of tyrosine degradation pathway 3-(4-hydroxyphenyl) pyruvate [c] -> CO_2 [c] + 3-(4-hyroxyphenyl) acetaldehyde [c] GPR: unknown EC 4.1.1.80	Addition of (4-hydroxyphenyl) pyruvate decarboxylase in the tyrosine degradation pathway. The ORF for the gene is unknown but this pathway is non-essential for viability hence adds to GG.	[7] [8]
	5	Addition of tyrosine degradation pathway 3-(4-hyroxyphenyl) acetaldehyde [c] + NADH [c] -> NAD^+ [c] + tyrosol [c] GPR: unknown EC 1.1.1.1	Addition of reduction reaction to form alcohol from aldehyde in tyrosine degradation pathway is similarly non-essential for viability and so GG.	[7] [8]
	6	Mitochondrial acetyl-transferase activity of glycine CoA [c] + L-2 amino 3-oxobutanoate [c] ⇔ acetyl-CoA [m] + L-glycine [m] GPR: *YDL040C or YGR147C or YHR013C*	• Correctly adds *NAT1, NAT2* and *ARD1* as GG cases.	[9] [10]
	7	GPR modification for reaction r_0195 Old GPR: *((YBR126C and YDR074W and YMR261C) or (YML100W and YBR126C and YDR074W))* New GPR: *((YBR126C and YDR074W and YMR261C and YML100W) or YBR126C)*	• *TPS1* gene is only essential in glucose media whereas both *TPS1* and *TPS2* genes are essential in galactose media reflected in old GPR • *TPS2* gene is restored as a GG from an ESG	[11] [12] [13]
	8	GPR modification for reaction r_1051 Old GPR: *((YBR126C and YDR074W and YMR261C) or (YML100W and YBR126C and YDR074W))* New GPR: *((YBR126C and YDR074W and YMR261C and YML100W) or YBR126C)*	• *TPS1* gene is only essential in glucose media whereas both *TPS1* and *TPS2* genes are essential in galactose media reflected in old GPR • *TPS2* gene is restored as a GG from an ESG	[11] [12] [13]
	9	GPR modification for reaction r_0995 Old GPR: *YDR023W or YHR011W*	• *SES1* gene is corrected from GES to ESES • *SES1-DIA1* is corrected from SL2ES and SL2G cases to	[14] [15]

GPR modifications

	New GPR: *YDR023W or (YDR023W and YHR011W)*	ESES and GG cases respectively.	
10	GPR modification for reaction r_0916 Old GPR: *((YHL011C and YKL181W) or (YOL061W and YBL068W) or (YOL061W and YER099C))* New GPR: *((YKL181W and YER099C) or (YKL181W and YHL011C) or (YKL181W and YBL068W) or (YER099C and YOL061W) or (YBL068W and YOL068W))*	• The new GPR suggests 4 new probable lethal triplet mutants namely: Δ*prs1*Δ*prs2*Δ*prs4*, Δ*prs1*Δ*prs2*Δ*prs5*, Δ*prs1*Δ*prs3*Δ*prs5*, Δ*prs2*Δ*prs3*Δ*prs4* and Δ*prs1*Δ*prs4*Δ*prs5*	[16]
11	GPR modification for reaction r_1178 Old GPR: *YMR319C* New GPR: *YMR319C or YMR058W*	• Iron (II) transporter across plasma membrane has 2 different genes encoding under low-affinity and high-affinity conditions • *FET4* gene is reconciled from ESG to GG • *FET3* gene is added to the model as a non-essential gene • *FET3-FET4 in vivo* lethal gene pair is correctly predicted by model now	[17]
12	GPR modification for reaction r_0250 Old GPR: *((YJR019C and YOR303W) or YJL130C)* New GPR: *YJR019C and YOR303W and YJL130C*	• SL2ES *CPA2-URA2* is resolved correctly to 2 ESES cases *CPA2* and *URA2* • SL2ES *CPA1-URA2* is resolved correctly to one more ESES case *CPA1* • At the same time it resolves 3 GES to ESES cases for the genes *CPA1*, *CPA2*, *URA2*	[18] [19]
13	GPR modification for reactions r_0886 and r_0887 along with suppression of PIT2m reaction (r_1245) due to Crabtree effect Old GPR: *YMR205C and YGR240C* New GPR: *YMR205C or (YGR240C and YMR205C)*	• Resolves *YDR050C-YMR205C* SL2ES case to ESES • Resolves *YDR050C-YGR240C* SL2G cases to GG • Resolves *YMR205C-YGR240C* GSL2 to SL2SL2 • Resolves *tpi1-fba1* SL2ES to ESES cases • Resolves *tpi1* from GES to ESES • Resolves *fba1* from GES to ESES	[20] [21]
14	GPR modification of reaction r_2116 Old GPR: *ALD2* New GPR: *ALD2 or ALD5 or ALD4*	• Resolves *ALD2* from SL2G to GG	[22]
		• Resolves *MAE1* from SL2G to GG	[23]
15	GPR modification of reaction r_0020 Old GPR: *YDR035W* New GPR: *YDR035W or YBR249C*		
17	GPR modification of reaction r_0116 Old GPR: *PHO11 or PHO5* New GPR: *PHO11 or PHO12 or PHO3 or PHO5*	• Adds genes *PHO5 and PHO12* to the model and correctly identified as GG	[24]

	18	GPR modification of reaction r_1237 Old GPR: *YOR130C* New GPR*: YOR130C or BAC1*	• Resolves *ORT1* from ESG to GG • Prediction of SL2U for *ORT1-BAC1*	[25]
	19	GPR modification for reaction r_0005 Old GPR: *YGR032W or YLR342W* New GPR: *(YGR032W or YLR342W) and (YCR034W or YLR372W)*	• Identifies *YCR034W-YLR372W* as SL2SL2 from GSL2 cases	[26]
	20	GPR modification for reaction r_0888 Old GPR: *YMR105C or YKL127W* New GPR: *(YMR105C or YKL127W) and (YMR105C or YKL127W or YMR278W)*	• Retains *PGM1-PGM2* SL2SL2 case and adds *PGM3* as a GG in the model.	[27]
Removal of reactions	21	Remove orphan reaction r_2031 It was initially suggested in *i*AZ900	Reconciles GSL2 of *fur1-ura3* case to SL2SL2	
	22	Remove reaction r_1682	Removes duplicate reaction, which is a lumped version of reactions r_0986, r_0243, r_0242, r_0244.	[28]
	23	Remove reaction r_0461	• Should not be present in *S. cerevisiae*, seen in *M. mazei* and also confirmed in UniProt.	[29]
Add genes to orphan reactions	24	Add an *E. coli* like *ubiC* gene for reaction r_1685. We call it here *Y-ubiC* gene. Chorismate [c] ⇔ 4-hydroxybenzoate [c] + pyruvate [c] GPR: unknown	• The ORF is unknown but the gene has been identified as GG. • Adds GPR to an orphan reaction	[30] [31] [32]
	25	Add genes for reaction r_0026 4-methyl thio-2-oxobutanoate [c] + L-glutamate [c] ⇔ 2-oxoglutarate [c] + L-methionine [c]	• Adds GPR: *YHR208W or YJR148W or YGL202W or YHR137W* where all 4 genes are correctly identified as GG	[33]
	26	Add genes for reaction r_0043 3-hexaprenyl-4-hydroxybenzoic acid [c] + 0.5 oxygen [c] ⇔ 3-hexaprenyl-4,5 dihydroxybenzoate [c]	Adds GPR: *YPL252C or YDR376W* Both the genes are correctly identified as GG	[34]
	27	Add genes for reaction r_0044 3-hexaprenyl-4-hydroxy-5-methoxybezoic acid [m] + H^+ [m] ⇔ 2-hexaprenyl-6-methoxyphenol [m] + CO_2 [m]	Adds GPR: *YDR538W and YDR539W* Both the genes are correctly identified as GG	[35]

28	Add genes for reaction r_0086 S-methyl-5-thio-D-ribulose 1-phosphate [c] ⇔ 5-methyl sulfanyl-2,3-dioxopentyl phosphate [c] + H_2O [c]	Adds GPR: *YJR024C* It is correctly identified as GG	[36]
29	Add genes for reaction r_0087 S-methyl-5-thio alpha ribose 1-phosphate [c] ⇔ S-methyl-5-thio-D-ribulose 1-phosphate [c]	Adds GPR: *YPR118W* It is correctly identified as GG	[33]
30	Add genes for reaction r_0094 L-alanine [c] +pimeloyl-CoA [c] ⇔ 8-amino-7 oxononanoate [c] + CO_2 [c] + CoA [c] + $4H^+$ [c]	• Adds GPR: *YAR069W-A or YHR214W-F* • Adds genes *BIO6* and *BIO8* putative genes to the model and both are correctly predicted as GG.	[37]
31	Add genes for reaction r_0475 H_2O [c] + L-glutamine [c] ⇔ ammonium [c] + L-glutamate [c]	• Adds GPR: *YMR096W or (YMR095C and YMR096W)* • Adds genes *SNZ1* and *SNO1* to the model Correctly identifies *SNZ1* and *SNO1* genes as GG	[38]
32	Add genes for reaction r_0992 Acetyl-CoA [c] + L-serine [c] ⇔ CoA [c] + O-acetyl-L-serine [c]	• Adds GPR: *(YDL040C and YGR147C and YHR013C) or (YDL040C and YGR147C)*	[39]
33	Add genes for reaction r_1623 5-formyltetrahydro folate [m] + ATP [m] ⇔ 5,10 methenyl-THF [m] + ADP [m] + P_i [m]	Adds GPR: *YER183C*	[40]
34	Add genes for reaction r_1624 5-formyltetrahydro folate [c] + ATP [c] + H_2O [c] ⇔ 10-formyl THF [c] + ADP [c] + P_i [c] + H^+ [c]	Adds GPR: *YER183C*	[40]
35	Adds GPR to reaction r_1603 GPR: *ADE5,7*	Correctly identified to be a GG	[41]
36	Adds GPR to reaction r_0696 GPR: *YOL151W (GRE2)*	Correctly identified to be a GG	[42]
37	Adds GPR to reaction r_1739 GPR: *PAA1*	Correctly identified to be a GG	[43]
38	Adds GPR to reaction r_1790 GPR: *YDL045C*	Correctly identified to be a GG	[44]

Table 2. Summary of results showing improvement of ES and SL prediction of *i*Sce926 over Yeast 7.11

Description	*i*Sce926	Yeast 7.11	Comments
Correct prediction of *in vivo* essential genes = ESES	92	72	*i*Sce926 shows 27.7% better performance than Yeast 7.11
Correct prediction of *in vivo* synthetic lethal genes = SL2SL2+SL3SL3	17	23	*i*Sce926 shows 35.2% better performance than Yeast 7.11
Reduction of erroneous prediction of *in vivo* non-essential genes = ESG	30	14	*i*Sce926 shows 53.3% reduction in erroneous prediction than Yeast 7.11
Suggested lethal knockout experiments (pairs and triples) = SL2U+SL3U	15	27	*i*Sce926 shows 80% increase in suggested gene deletion experiments than Yeast 7.11
Selectivity= ESES/(ESES+GES)	0.347	0.288	*i*Sce926 shows 20.4% increase in selectivity than Yeast 7.11
Specificity= GG/(GG+ESG)	0.951	0.977	*i*Sce926 shows 2.7% increase in specificity than Yeast 7.11

Table 3. Full version of Table 6 showing agreement, disagreement with *in vivo* data and model modifications in CHO 1.2

		Gene name	Comments	Modifications	Reference
Single Gene Deletion	Match between *in vivo* and *in silico*	*acsL3*	Δ*acsL3* strain has an impaired Liver-X Receptor/ Retinoid-X Receptor signalling pathway in CHO cells. CHO-K1 cell lines show mutant strains have impaired lipid biosynthesis. *In silico* mutant strain shows sphingomyelin auxotrophy. However, *in vivo* lethality endorses *in silico* predictions.		[45] [46] [45]
		ggypS1	Δ*ggypS1* strain has an impaired carotenoid biosynthesis *in vivo.* Similarly, mouse and human Δ*ggypS1* cell lines were also found to be inviable since it is an important G-protein precursor. *In silico* mutant strain is cholesterol auxotroph, hence inviable. Thus *in vivo* result matches *in silico* predictions.		[47] [48] [47]
		fasN	*fasN* gene is shown to be highly conserved in mammalian systems. Δ*fasN* strain has been shown to shut off the lipid biosynthesis and hence renders the strain inviable in mouse. It can be extrapolated as a compliance of *in vivo* and *in silico* results.		[49] [50]
		hmgCr	*hmgCr* gene shows more than 80% homology in CHO cells with humans and mouse counterparts. *In vivo* mouse and *in silico* CHO Δ*hmgCr* strains are cholesterol auxotrophs and thus affirm conformation.		[51]
	Mismatch between *in vivo* and *in silico*	*dhfr*	Deletion of *dhfr* prevents biomass precursor sphingomyelin formation *in silico*, However, this deletion is not lethal in vivo in CHO-K1 cell lines.		[46]
		gys1	Δ*gys1 in silico* mutant strain is glycogen auxotroph. *in vivo* studies show *gys1*- mutant is viable and forms SL2 with *gys2.*	GPR modified from: *(gys1 and gys2)* to *(gys1 or gys2)* *gys1* and *gys2* reconciled from ESG to GG *gys1-gys2* reconciles from ESG to SL2SL2	[52] [53] [54]
		acsL1, acsL3, acsL4	Δ*acsL4 in silico* mutant is sphingomyelin auxotroph. However, *in vivo* data for mouse reveals that *acsL4* deletion is viable.	r_0147 and r_0148 GPR was modified from *acsL4* to *(acsL1 or acsL3 or acsL4)* r_0142 GPR was modified from *acsL1* to *(acsL1 or acsL3 or acsL4)* r_0146 GPR was modified from *acsL3 to (acsL1 or acsL3 or acsL4)* *acsL1, acsL3* and *acsL4* were fixed from ESG to GG	[55]
		afmld	Δ*afmld in silico* mutant is sphingomyelin auxotroph. However, *in vivo* data for mouse reveals that *afmld* deletion is viable.		[56]

Single gene deletion Suggestion for CHO-K1 single gene deletion	*arg1*	Δ*arg1* mutant *in silico* is spermidine and putrescine auxotroph. Mouse knockout experiments show that it is *in vivo* essential. But due to lack of gene homology information, this serves as an important suggestion for an experimentalist to perform in CHO-K1 cell line.		[57]
	mthFr	Δ*mthFr* mutant *in silico* is 5-methyl tetrahydrofolate auxotroph and hence inviable. Mouse knockout experiments show that it is *in vivo* essential. Unavailability of homology information makes it an important suggestion for CHO-K1 single gene deletion candidate.		[58]
	qprT	Δ*qprT* mutant *in silico* causes auxotrophy of cofactors NAD^+, NADH, $NADP^+$ and NADPH. No experimental evidence of knockout data exists in CHO-K1 cell line. This serves as a potential non-intuitive essential gene.		NA[1]
	ugp2	Δ*ugp2* mutant *in silico* causes glycogen auxotrophy. No experimental evidence of CHO-K1 knockout data for *ugp2* exists. This makes it an important suggestion for single gene knockout studies. .		NA
Double gene deletion Mismatches with experimental evidence	*pgm1-pgm2*	Δ*pgm1*Δ*pgm2* double mutant is lethal *in silico* causing glycogen auxotrophy. However, single gene mouse deletion shows Δ*pgm2* strain is inviable and there is more than 80% homology in mouse and CHO *pgm2.*	GPR modification from *pgm1 or pgm2* to *pgm2 or (pgm1 and pgm2)*. *pgm2* is fixed from GES to ESES SL2ES case is fixed to ESES	[59]
	pcyT1a-pcyT1b	Δ*pcyT1a*Δ*pcyT1b* double mutant causes phosphatidylcholine and sphingomyelin auxotrophy *in silico*. However, *in vivo* studies reveal that *pcyT1a* deletion alone is seen to be lethal in mouse.	Changing GPR for phoshphate cytidyltransferase reaction (r_1023) from *pcyT1a or pcyT1b* to *pcyT1a or (pcyT1a and pcyT1b)* resolves SL2ES to ESES and GES to ESES with respect to *pcyT1a.*	[60]
	chkA-chkB	Δ*chkA* mouse strains have been shown to be embryonic lethal. However Δ*chkB* deletions have been non-lethal.	Changing GPR for choline-kinase reactions r_0359 and r_0360 from *chkA or chkB* to *chkA or (chkA and chkB)* resolved SL2ES to ESES and GES to ESES with respect to *chkA*	[61]
Suggested CHO-K1 experiments	*slc14a1-slc14a2*	Δ*slc14a1*Δ*slc14a2* double mutant has been shown to be spermidine and putrescine auxotroph. In a mouse *in silico* reconstruction[2] this has been shown to be lethal pair as well. But there are no experimental evidence so it goes as a suggestion.		NA
	dhcR24-choL4	Δ*dhcR24*Δ*choL4* double mutant is cholesterol auxotroph in both CHO 1.2 and mouse *in silico* models. However no experimental single or double deletion data exists.		NA

	Suggested CHO-K1 experiments	*ptdSs1-ptdSs2*	Δ*ptdSs1*Δ*ptdSs2* is incapable of *in silico* production of phosphatidylserine and phosphatidylethanolamine. The mouse GSM also confirms this *in silico* lethal pair. However no experimental single or double deletion data exists in either CHO-K1 or mouse.	NA
		gusB-impA2	Δ*gusB*Δ*impA2* is incapable of *in silico* production of 1-phosphatidyl-D-myoinositol. The mouse GSM also confirms this *in silico* lethal pair. However no experimental single or double deletion data exists in either CHO-K1 or mouse.	NA
Higher order gene deletions	Suggested CHO-K1 experiments	*dhoDh-fh1-cytB*	Δ*dhoDh*Δ*fh1*Δ*cytB* triple mutants are incapable of Sphingomyelin production *in silico.* Neither *in silico* higher gene deletion information was available from the mouse model nor do we have any mouse or CHO *in vivo* triple knockout information.	NA
		ggh-pipOx-slc19a1	Δ*ggh*Δ*pipOx*Δ*slc19a1* triple mutants are incapable of 5 methyl tetrahydrofolate production *in silico.* Neither *in silico* higher gene deletion information was available from the mouse model nor do we have any mouse or CHO *in vivo* triple knockout information.	NA
		cox(N)-dhoDh-sdhD	Δ*cox(N)*Δ*dhoDh*Δ*sdhD* triple mutants are incapable of Sphingomyelin production *in silico.* Neither *in silico* higher gene deletion information was available from the mouse model nor do we have any mouse or CHO *in vivo* triple knockout information. N belongs to {1, 2, 3, 5a, 5b, 6a1, 6a2, 6b1, 6b2, 6c, 7a1, 7a2, 7a2l, 7b, 7c, 8a, 8b} This particular example points to 18 *in silico* lethal triplets, but we have explained them in results as a single case.	NA
		nanS-npl-st8Sia1 -st8Sia5	Δ*nanS*Δ*npl*Δ*st8Sia1*Δ*st8Sia5* quadruple mutants are incapable of N-acetylneuraminate production *in silico.* Neither *in silico* higher gene deletion information was available from the mouse model nor do we have any mouse or CHO *in vivo* quadruple knockout information.	NA
		ak1-ak2-ak3L1 -cmpK1	Δ*ak1*Δ*ak2*Δ*ak3L1*Δ*cmpK1* quadruple mutants are incapable of phosphatidylglycerol, phosphatidylserine, phosphatidylethanolamine, phosphatidylcholine, cardiolipin, 1-phosphatidyl-D-myoinositol production *in silico.* Neither *in silico* higher gene deletion information was available from the mouse model nor do we have any mouse or CHO *in vivo* quadruple knockout information.	NA

polA1-rrm1-rrm2 -rrm2b	Δ*polA1*Δ*rrm1*Δ*rrm2*Δ*rrm2b* quadruple mutants are incapable of d-ATP, d-TTP, d-CTP and d-GTP production *in silico.* Neither *in silico* higher gene deletion information was available from the mouse model nor do we have any mouse or CHO *in vivo* quadruple knockout information.	NA	

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