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Life Sciences Reporting Summary

Comments Prepared By:

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Natalie received her B.S. in Biomedical Engineering from Boston University, where she studied the prediction and validation of transmembrane protein structures in the Golgi apparatus using bioinformatics tools and molecular biology techniques. She earned her M.S. and Ph.D. from University of California, San Diego, where she specialized in systems biology and examined the metabolic networks of eukaryotic organisms. Natalie constructed a genome-scale computational model of human cell metabolism that integrated over 50 years of legacy data and the human genome annotation. She has also performed research on head injury potential in snowboarding accidents using anthropomorphic test devices.

Reporting Summary – Extended Comments

General comments:

• Wherever statistics have been derived (e.g., error bars, box plots, statistical significance), the legend needs to provide and define the n number (i.e., the sample size used to derive statistics) as a precise value (not a range), using the wording "n=X biologically independent samples/animals/independent experiments," etc. as applicable.

• All error bars need to be defined in the legends (e.g., SD, SEM) together with a measure of centre (e.g., mean, median), and should be accompanied by their precise n number defined as noted above.

• All box plots need to be defined in the legends in terms of minima, maxima, centre, and percentiles, and should be accompanied by their precise n number defined as noted above.

• The figure legends must indicate the statistical test used, whether the test was one- or two-sided and whether adjustments were made for multiple comparisons (if applicable).

• Test results (e.g., P values) should be given as exact values whenever possible and appropriate, and confidence intervals noted.

• For null hypothesis testing, please indicate the test statistic (e.g., F, t, r) with confidence intervals, effect sizes, degrees of freedom and P values noted.

• In all cases where the number of data points is <10, individual data points must be shown.

Specific comments:

Figure 1c-d

• Please state the statistical test used. If applicable, indicate whether the test was one- or two-sided and whether adjustments were made for multiple comparisons.

• The p value has been provided as a range; please provide the precise value if possible and appropriate.

Figure 1e

• Please provide and define the sample size (n) in the figure legend as described in the General comments above.

• Please define the box plots in the figure legend according to the General comments provided above.

Figure 1f

• Please provide and define the sample size (n) in the figure legend as described in the General comments above.

• Please state the statistical test used. If applicable, indicate whether the test was one- or two-sided and whether adjustments were made for multiple comparisons.

• The p value has been provided as a range; please provide the precise value if possible and appropriate.

Figure 2b

• Please define the measure of centre (e.g., median or mean) in the figure legend.

• Please overlay each data point as dot plots to indicate the distribution of the data.

Figure 3a

• Please provide and define the sample size (n) in the figure legend as described in the General comments above.

• Please state the statistical test used. If applicable, indicate whether the test was one- or two-sided and whether adjustments were made for multiple comparisons.

Figure 3i-j

• Please provide and define the sample size (n) in the figure legend as described in the General comments above.

Figure 4a

• Please provide and define the sample size (n) in the figure legend as described in the General comments above.

• Please define the box plots in the figure legend according to the General comments provided above.

• Please state the statistical test used. If applicable, indicate whether the test was one- or two-sided and whether adjustments were made for multiple comparisons.

• The p value has been provided as a range; please provide the precise value if possible and appropriate.

Figure 4g

• Please define the box plots in the figure legend according to the General comments provided above.

• Please indicate in the figure legends whether the statistical tests were one-sided or two-sided.

• The p value has been provided as a range; please provide the precise value if possible and appropriate.

• Please define the "*" notation in the figure legend.

• Please overlay each data point as dot plots to indicate the distribution of the data.

Figure 6a-c

• Please provide and define the sample size (n) in the figure legend as described in the General comments above.

• Please define the box plots in the figure legend according to the General comments provided above.

• Please state the statistical test used. If applicable, indicate whether the test was one- or two-sided and whether adjustments were made for multiple comparisons.

• The p value has been provided as a range; please provide the precise value if possible and appropriate.

Figure S1b

• Please provide and define the sample size (n) in the figure legend as described in the General comments above.

• Please define the centre values and error bars in the figure legend.

Figure S3a-d

• Please state the statistical test used. If applicable, indicate whether the test was one- or two-sided and whether adjustments were made for multiple comparisons

• The p value has been provided as a range; please provide the precise value if possible and appropriate.

Figure S7a-e

• Please provide and define the sample size (n) in the figure legend as described in the General comments above.

• Please define the box plots in the figure legend according to the General comments provided above.

Figure S12a-f

• Please provide and define the sample size (n) in the figure legend as described in the General comments above.

• Please define the box plots in the figure legend according to the General comments provided above.

• Please define the letter notation in the legend.

• If the letter notation denotes statistical significance, please state the statistical test and whether it was one- or two-sided.

• If the letter notation denotes statistical significance, please provide a precise p value if possible and appropriate.

Figure S13a-c

• Please provide and define the sample size (n) in the figure legend as described in the General comments above.

• Please define the box plots in the figure legend according to the General comments provided above.

• Please state the statistical test used. If applicable, indicate whether the test was one- or two-sided and whether adjustments were made for multiple comparisons.

• The p value has been provided as a range; please provide the precise value if possible and appropriate.

Table S1

• Please provide and define the sample size (n) in the figure legend as described in the General comments above.

• Please define the measure of centre (e.g. median or mean) and measure of error (e.g., SD, SEM) in the figure legend.

Table S4

• Please provide and define the sample size (n) in the figure legend as described in the General comments above.

• Please state the statistical test used. If applicable, indicate whether the test was one- or two-sided and whether adjustments were made for multiple comparisons.

Table S6

• Please provide and define the sample size (n) in the figure legend as described in the General comments above.

• Please state the statistical test used. If applicable, indicate whether the test was one- or two-sided and whether adjustments were made for multiple comparisons.

Table S8

• Please provide and define the sample size (n) in the figure legend as described in the General comments above.

• Please state the statistical test used. If applicable, indicate whether the test was one- or two-sided and whether adjustments were made for multiple comparisons.

Table S9

• Please provide and define the sample size (n) in the figure legend as described in the General comments above.

• Please state the statistical test used. If applicable, indicate whether the test was one- or two-sided and whether adjustments were made for multiple comparisons.

Editorial Policy Checklist – Extended Comments

No additional comments.

Notes to the Editor

A search for BioProject: PRJCA001214 yielded no results. An author request was made to ensure that all data are publicly available prior to publication.

The data and code availability statements have been combined in an Accession numbers section. An author request was made to include the code availability statement in a Code availability section in the Methods.