

## **Electronic supplementary information**

### **of**

#### **A translational approach to assess the metabolomic impact of stabilized gold nanoparticles by NMR spectroscopy**

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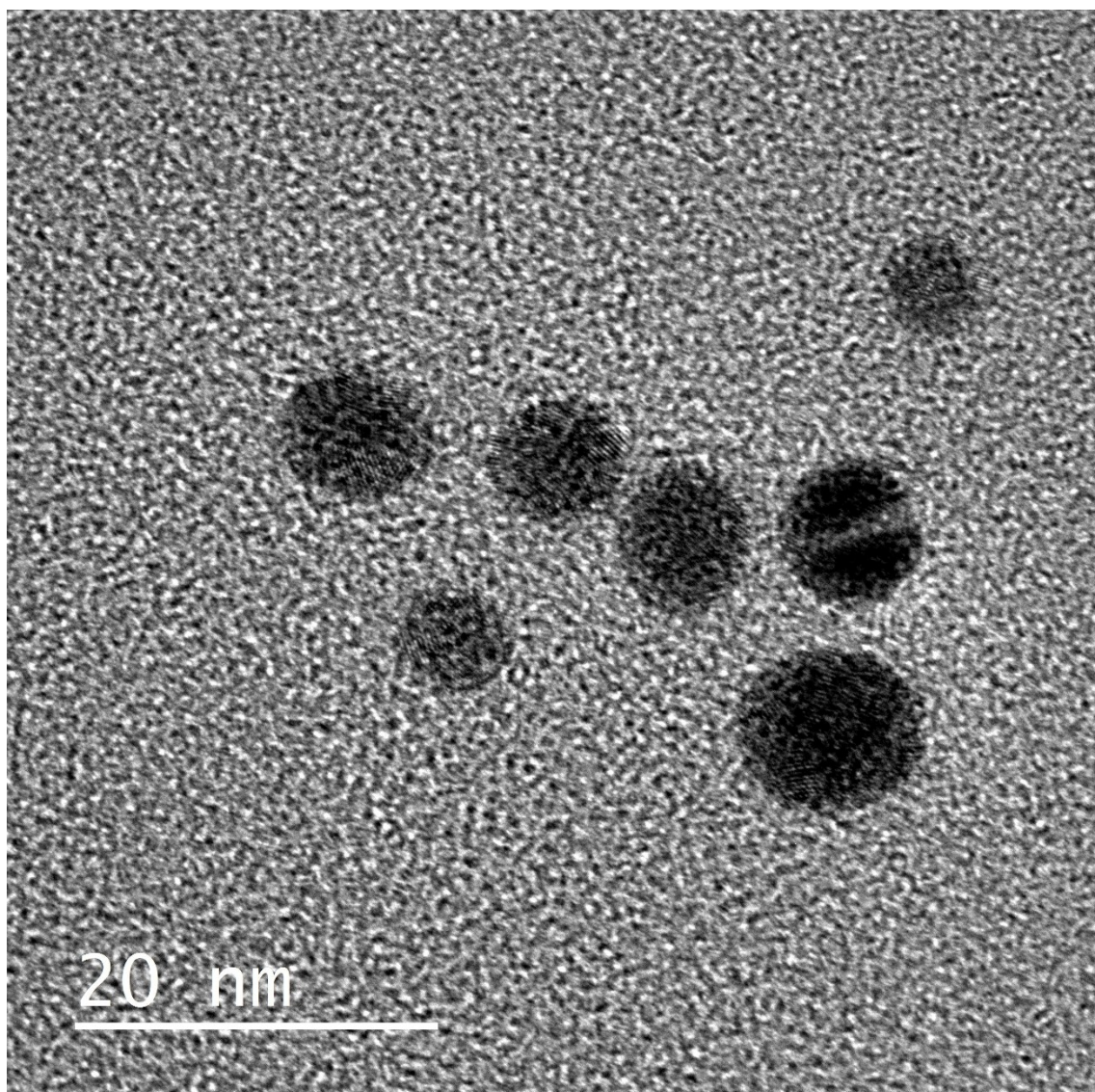
d Instituto de Investigación Sanitaria La Fe, Hospital Universitario i Politécnico La Fe, Valencia, Spain.

e Centro de Investigación Príncipe Felipe, Valencia, Spain.

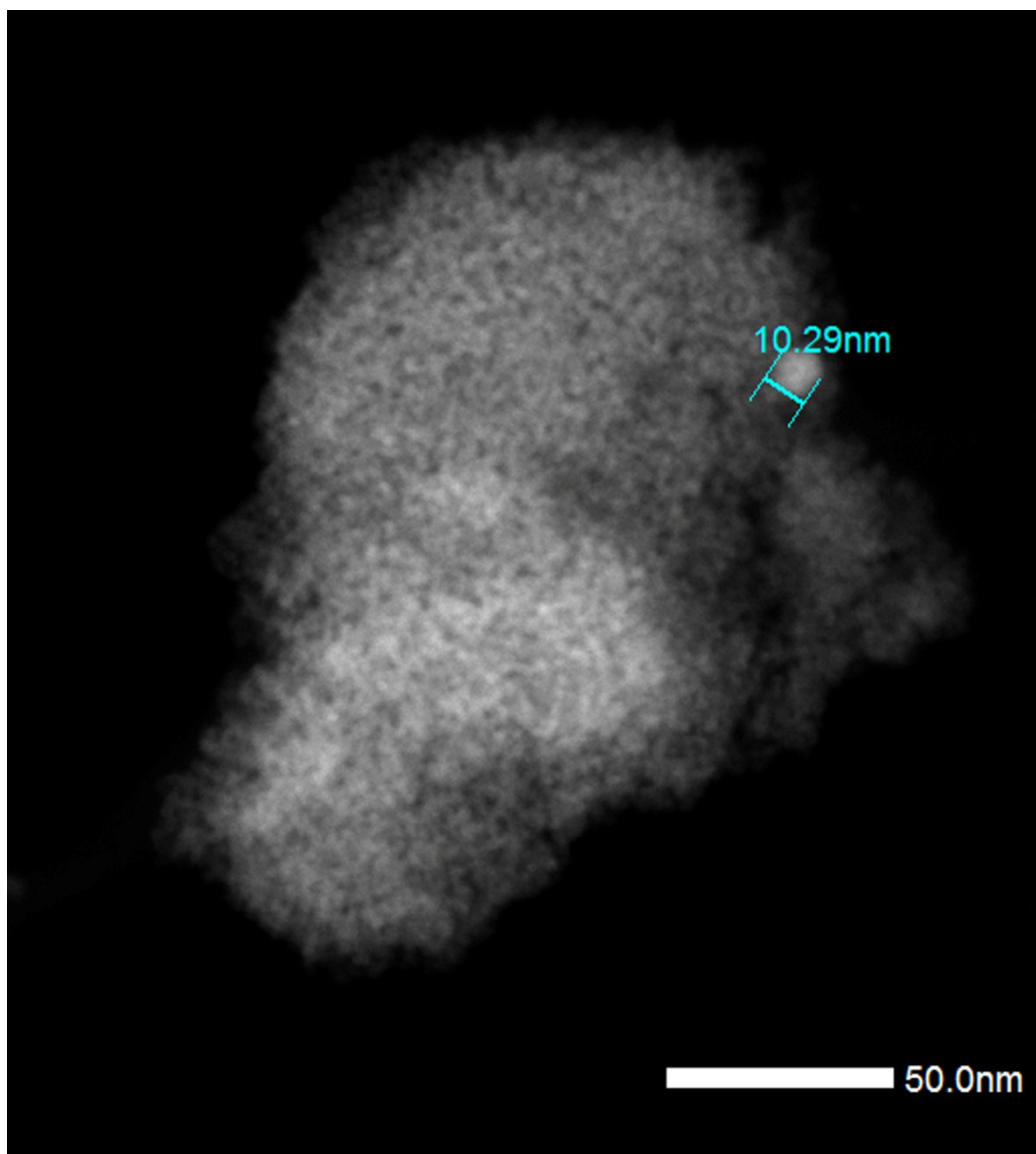
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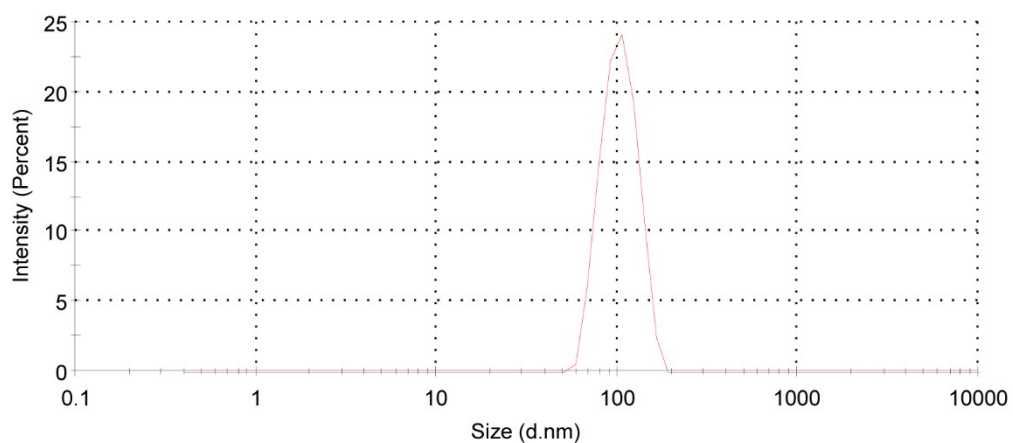
E-mail: raul.herance@vhir.org



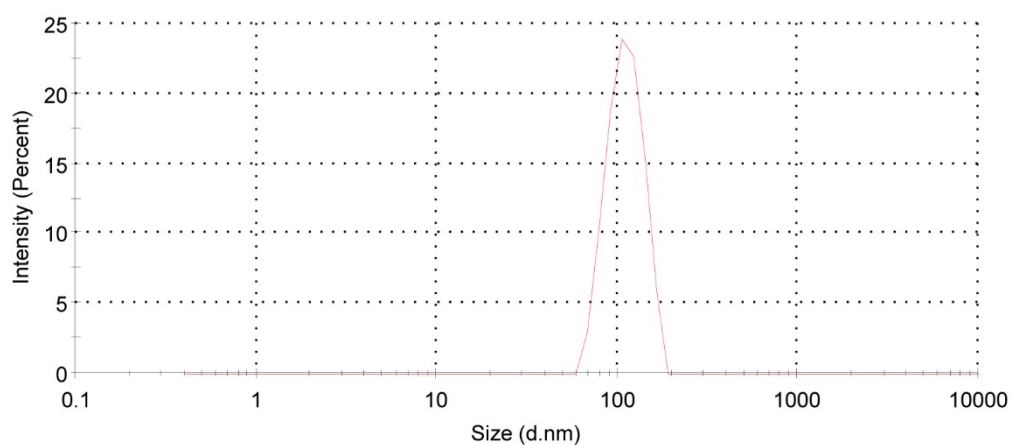
**Supplementary Figure 1.** TEM recorded for AuChi. The average size of Au NPs coated with chitosan was determined with 100 measures of NPs.



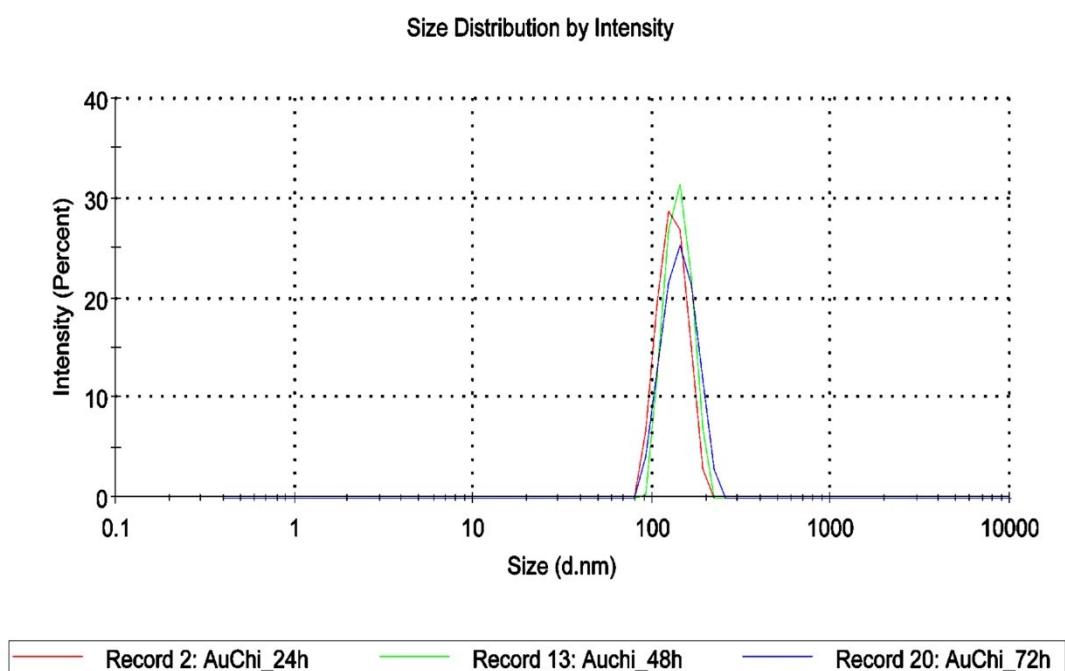
**Supplementary Figure 2.** TEM recorded for AuCeO<sub>2</sub>. The average size of Au NPs coated with chitosan was determined with 100 measures of NPs.



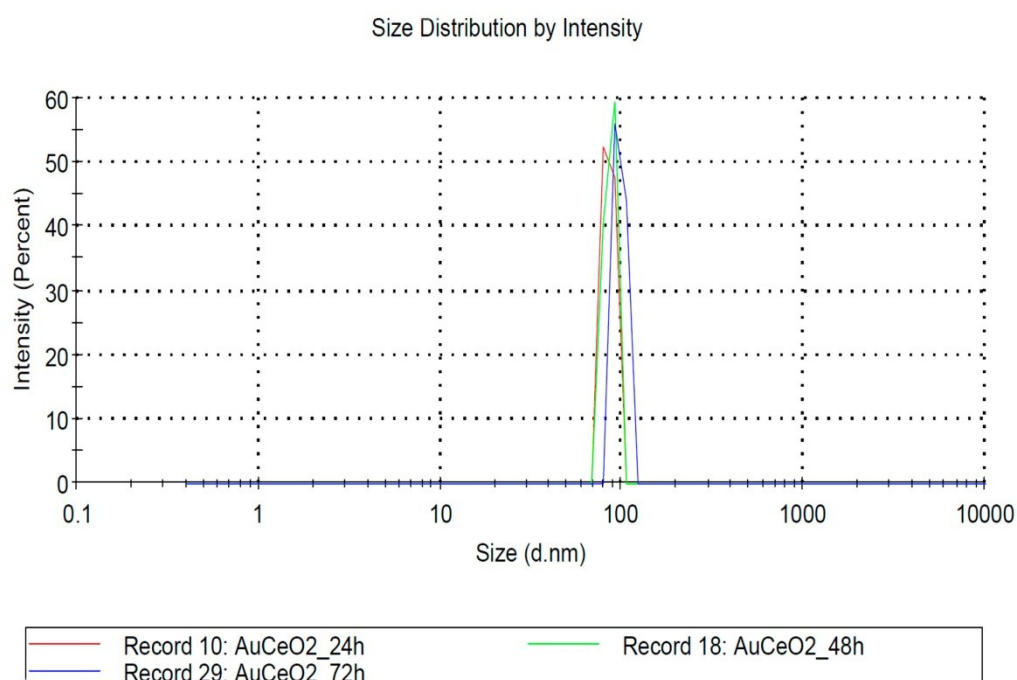
**Supplementary Figure 3.** DLS recorded for AuChi. The analysis performed to determine the hydrodynamic size was done using a 20  $\mu\text{g/mL}$  solution of AuChi in PBS.



**Supplementary Figure 4.** DLS recorded for AuCeO<sub>2</sub>. The analysis performed to determine the hydrodynamic size was done using a 20  $\mu\text{g/mL}$  solution of AuCeO<sub>2</sub> in PBS.

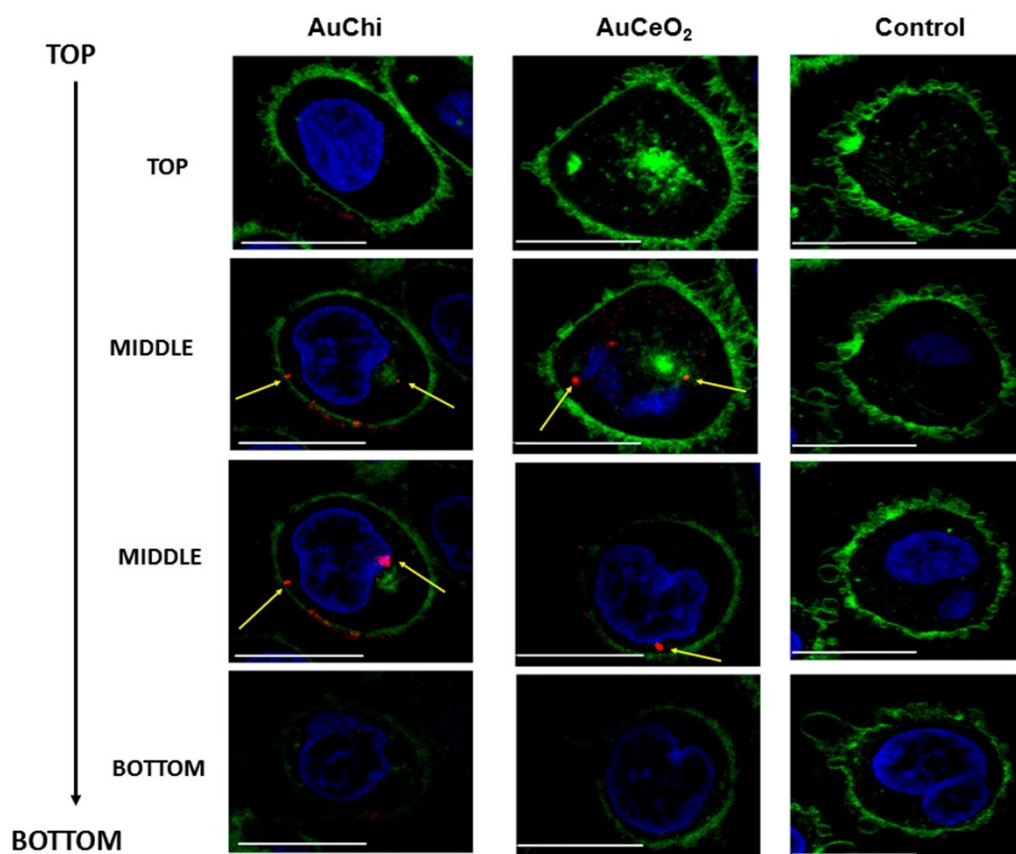


**Supplementary Figure 5.** Dynamic light scattering spectra to determine the hydrodynamic size and the stability of AuChi nanoparticles at 24h, 48h and 72 hours diluted in PBS, final concentration 20  $\mu\text{g/ml}$ .

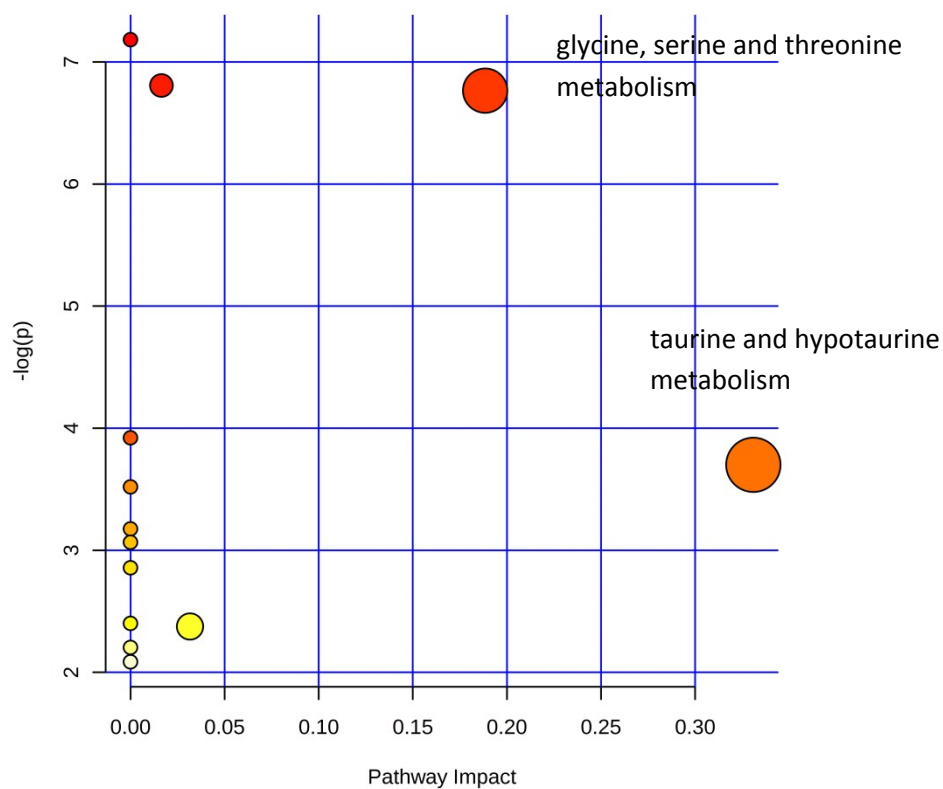


**Supplementary Figure 6.** Dynamic light scattering spectra to determine the hydrodynamic size and the stability of AuCeO<sub>2</sub> nanoparticles at 24h, 48h and 72 hours diluted in PBS, final concentration 20  $\mu\text{g/ml}$ . A) AuChi, B) AuCeO<sub>2</sub>.



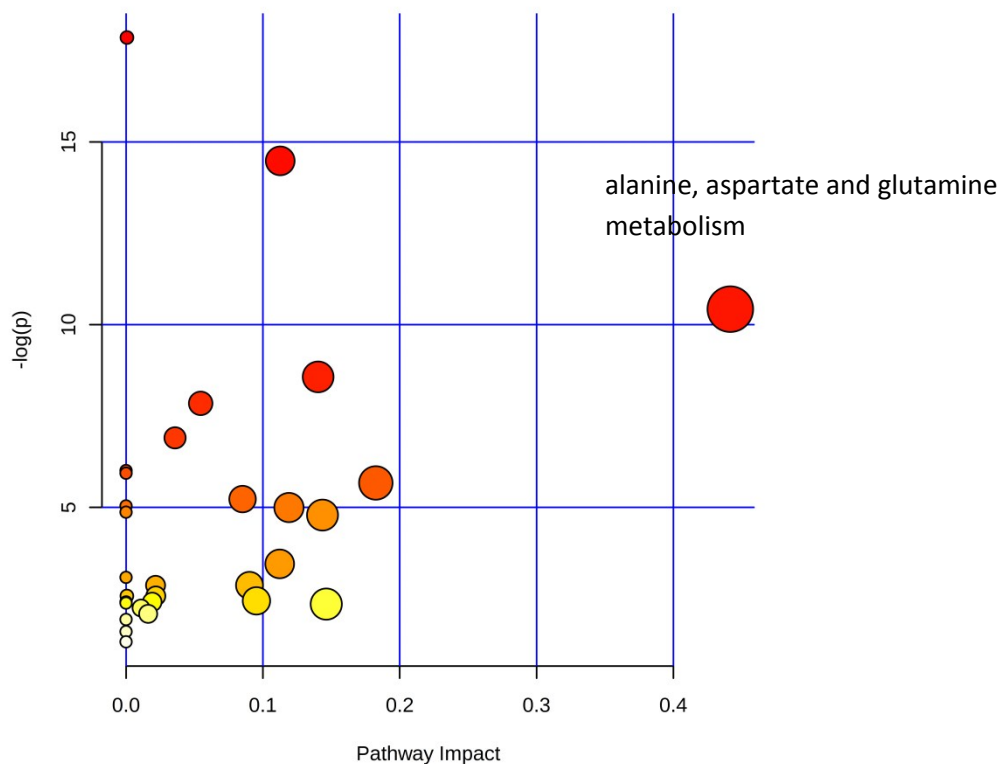


**Supplementary Figure 7.** Z-axis scanning images of AuChi, AuCeO<sub>2</sub> and without NPs (control) in HeLa cells by laser confocal microscope obtained merging the blue (Hoechst) to label the nucleus, and green (CellMask) to label the cellular membrane. Fluorescence were obtained exciting at 405 nm (exciting Hoechst, blue), and 488 nm (exciting CellMask, green) and the emission was collected from 415 to 550 nm in separate channels. The red spots indicating the location of NPs after irradiating at 633 nm (yellow arrows). Scale bars are 20 μm in all cases.



| Pathway                                 | Expected | Total    | Hits | Raw p      | -log(p) | Holm adjust | FDR      | Impact  |
|-----------------------------------------|----------|----------|------|------------|---------|-------------|----------|---------|
| Nitrogen metabolism                     | 39       | 0,048608 | 2    | 0,00075984 | 7,1824  | 0,060787    | 0,030767 | 0       |
| Primary bile acid biosynthesis          | 47       | 0,058579 | 2    | 0,001106   | 6,807   | 0,087374    | 0,030767 | 0,01644 |
| Glycine serine and threonine metabolism | 48       | 0,059826 | 2    | 0,0011538  | 6,7647  | 0,089993    | 0,030767 | 0,18845 |
| Cyanoamino acid metabolism              | 16       | 0,019942 | 1    | 0,019818   | 3,9212  | 1           | 0,39504  | 0       |
| Taurine and hypotaurine metabolism      | 20       | 0,024927 | 1    | 0,024731   | 3,6997  | 1           | 0,39504  | 0,33094 |
| Thiamine metabolism                     | 24       | 0,029913 | 1    | 0,029628   | 3,519   | 1           | 0,39504  | 0       |
| Methane metabolism                      | 34       | 0,042376 | 1    | 0,041798   | 3,1749  | 1           | 0,46637  | 0       |
| Glutathione metabolism                  | 38       | 0,047362 | 1    | 0,046637   | 3,0654  | 1           | 0,46637  | 0       |
| Lysine degradation                      | 47       | 0,058579 | 1    | 0,057466   | 2,8566  | 1           | 0,51081  | 0       |
| Aminoacyl-tRNA biosynthesis             | 75       | 0,093477 | 1    | 0,090631   | 2,401   | 1           | 0,67615  | 0       |
| Arginine and proline metabolism         | 77       | 0,09597  | 1    | 0,09297    | 2,3755  | 1           | 0,67615  | 0,03163 |
| Purine metabolism                       | 92       | 0,11467  | 1    | 0,11038    | 2,2038  | 1           | 0,73589  | 0       |
| Porphyrin and chlorophyll metabolism    | 104      | 0,12962  | 1    | 0,12415    | 2,0863  | 1           | 0,76401  | 0       |

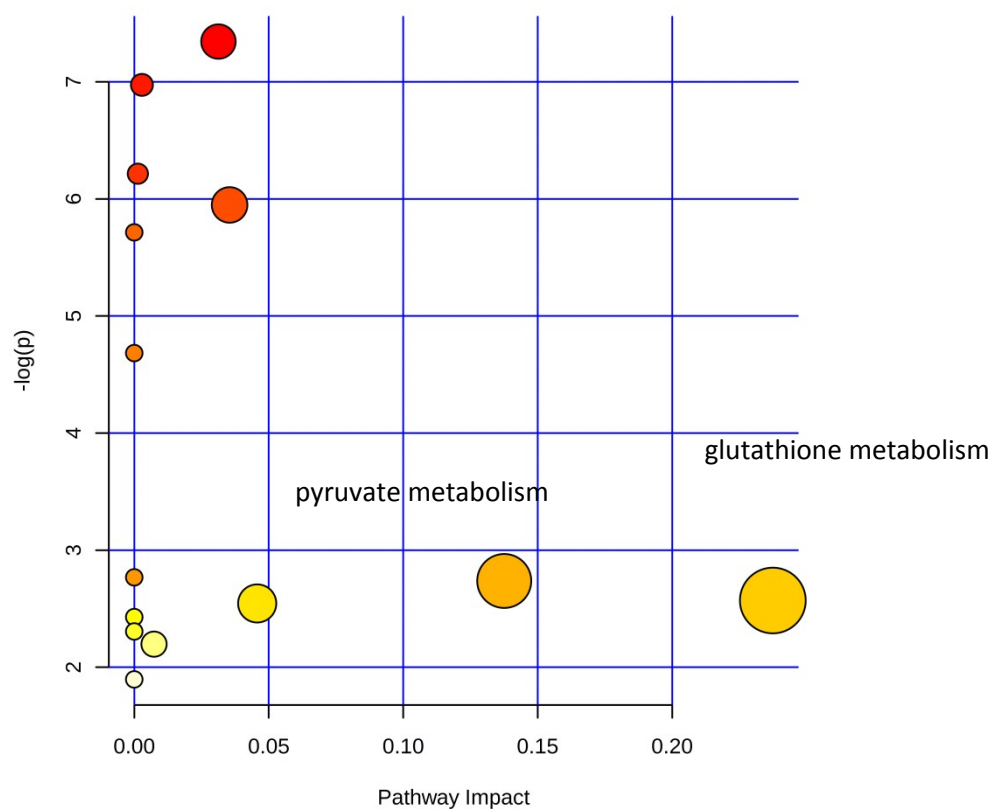
**Supplementary Figure 8.** Metabolic routes altered by AuChi and AuCeO<sub>2</sub> particles, at similar time points.



| Pathway                                            | Expected | Total    | Hits | Raw p      | -log(p) | Holm adjust | FDR        | Impact  |
|----------------------------------------------------|----------|----------|------|------------|---------|-------------|------------|---------|
| Nitrogen metabolism                                | 39       | 0,11342  | 5    | 1,76E-08   | 17,855  | 1,41E-06    | 1,41E-06   | 0,00067 |
| Aminoacyl-tRNA biosynthesis                        | 75       | 0,21811  | 5    | 5,15E-07   | 14,48   | 4,07E-05    | 2,06E-05   | 0,11268 |
| Alanine aspartate and glutamate metabolism         | 24       | 0,069796 | 3    | 2,97E-05   | 10,424  | 0,0023186   | 0,00079267 | 0,4416  |
| Histidine metabolism                               | 44       | 0,12796  | 3    | 0,00018967 | 8,5702  | 0,014605    | 0,0037935  | 0,14039 |
| Cysteine and methionine metabolism                 | 56       | 0,16286  | 3    | 0,00039102 | 7,8468  | 0,029717    | 0,0062563  | 0,05455 |
| Arginine and proline metabolism                    | 77       | 0,22393  | 3    | 0,0010047  | 6,903   | 0,075355    | 0,013396   | 0,03582 |
| Pantothenate and CoA biosynthesis                  | 27       | 0,078521 | 2    | 0,0024587  | 6,0081  | 0,18194     | 0,026441   | 0       |
| beta-Alanine metabolism                            | 28       | 0,081429 | 2    | 0,0026441  | 5,9354  | 0,19302     | 0,026441   | 0       |
| Pyruvate metabolism                                | 32       | 0,093062 | 2    | 0,0034503  | 5,6693  | 0,24842     | 0,030669   | 0,18254 |
| Butanoate metabolism                               | 40       | 0,11633  | 2    | 0,0053657  | 5,2277  | 0,38096     | 0,042925   | 0,08516 |
| Nicotinate and nicotinamide metabolism             | 44       | 0,12796  | 2    | 0,0064714  | 5,0404  | 0,453       | 0,045086   | 0       |
| Phenylalanine metabolism                           | 45       | 0,13087  | 2    | 0,006763   | 4,9963  | 0,46664     | 0,045086   | 0,11906 |
| Glycine serine and threonine metabolism            | 48       | 0,13959  | 2    | 0,0076735  | 4,87    | 0,5218      | 0,047222   | 0       |
| Glyoxylate and dicarboxylate metabolism            | 50       | 0,14541  | 2    | 0,0083101  | 4,7903  | 0,55678     | 0,047486   | 0,14359 |
| D-Glutamine and D-glutamate metabolism             | 11       | 0,03199  | 1    | 0,031594   | 3,4548  | 1           | 0,1685     | 0,1123  |
| Cyanoamino acid metabolism                         | 16       | 0,046531 | 1    | 0,045669   | 3,0863  | 1           | 0,22835    | 0       |
| Taurine and hypotaurine metabolism                 | 20       | 0,058164 | 1    | 0,056803   | 2,8682  | 1           | 0,25246    | 0,02158 |
| Citrate cycle (TCA cycle)                          | 20       | 0,058164 | 1    | 0,056803   | 2,8682  | 1           | 0,25246    | 0,09024 |
| Phenylalanine tyrosine and tryptophan biosynthesis | 27       | 0,078521 | 1    | 0,076019   | 2,5768  | 1           | 0,292      | 0,00062 |
| Valine leucine and isoleucine biosynthesis         | 27       | 0,078521 | 1    | 0,076019   | 2,5768  | 1           | 0,292      | 0,02173 |
| Glycolysis or Gluconeogenesis                      | 31       | 0,090154 | 1    | 0,086848   | 2,4436  | 1           | 0,292      | 0,0953  |
| Pentose phosphate pathway                          | 32       | 0,093062 | 1    | 0,089539   | 2,4131  | 1           | 0,292      | 0       |
| Lysine biosynthesis                                | 32       | 0,093062 | 1    | 0,089539   | 2,4131  | 1           | 0,292      | 0       |
| Vitamin B6 metabolism                              | 32       | 0,093062 | 1    | 0,089539   | 2,4131  | 1           | 0,292      | 0,01914 |
| Terpenoid backbone biosynthesis                    | 33       | 0,09597  | 1    | 0,092222   | 2,3836  | 1           | 0,292      | 0       |
| Methane metabolism                                 | 34       | 0,098878 | 1    | 0,094899   | 2,3549  | 1           | 0,292      | 0,14633 |
| Glutathione metabolism                             | 38       | 0,11051  | 1    | 0,10554    | 2,2487  | 1           | 0,31271    | 0,01095 |
| Ascorbate and aldarate metabolism                  | 45       | 0,13087  | 1    | 0,1239     | 2,0883  | 1           | 0,354      | 0,01617 |
| Pentose and glucuronate interconversions           | 53       | 0,15413  | 1    | 0,14449    | 1,9346  | 1           | 0,39858    | 0       |
| Tyrosine metabolism                                | 76       | 0,22102  | 1    | 0,20138    | 1,6026  | 1           | 0,53702    | 0       |
| Porphyrin and chlorophyll metabolism               | 104      | 0,30245  | 1    | 0,26624    | 1,3234  | 1           | 0,68707    | 0       |

**Supplementary Figure 9.** Metabolic routes altered by AuChi and AuCeO2 particles, at different time points (48 h for AuChi and 72 h for AuCeO2).





| Pathway                                    | Expected | Total    | Hits | Raw p      | -log(p) | Holm adjust | FDR      | Impact  |
|--------------------------------------------|----------|----------|------|------------|---------|-------------|----------|---------|
| Citrate cycle (TCA cycle)                  | 20       | 0,041545 | 2    | 0,00064639 | 7,3441  | 0,051711    | 0,037434 | 0,0313  |
| Alanine aspartate and glutamate metabolism | 24       | 0,049855 | 2    | 0,00093584 | 6,9741  | 0,073931    | 0,037434 | 0,00285 |
| Propanoate metabolism                      | 35       | 0,072705 | 2    | 0,001999   | 6,2151  | 0,15592     | 0,052192 | 0,00134 |
| Butanoate metabolism                       | 40       | 0,083091 | 2    | 0,0026096  | 5,9486  | 0,20094     | 0,052192 | 0,03545 |
| Phenylalanine metabolism                   | 45       | 0,093477 | 2    | 0,0032983  | 5,7144  | 0,25067     | 0,052773 | 0       |
| Tyrosine metabolism                        | 76       | 0,15787  | 2    | 0,0092504  | 4,6831  | 0,69378     | 0,12334  | 0       |
| Glycolysis or Gluconeogenesis              | 31       | 0,064396 | 1    | 0,062809   | 2,7677  | 1           | 0,62795  | 0       |
| Pyruvate metabolism                        | 32       | 0,066473 | 1    | 0,064781   | 2,7367  | 1           | 0,62795  | 0,13756 |
| Glutathione metabolism                     | 38       | 0,078936 | 1    | 0,076545   | 2,5699  | 1           | 0,62795  | 0,23743 |
| Glycerophospholipid metabolism             | 39       | 0,081014 | 1    | 0,078494   | 2,5447  | 1           | 0,62795  | 0,04571 |
| Nicotinate and nicotinamide metabolism     | 44       | 0,0914   | 1    | 0,08819    | 2,4283  | 1           | 0,64138  | 0       |
| Glyoxylate and dicarboxylate metabolism    | 50       | 0,10386  | 1    | 0,099717   | 2,3054  | 1           | 0,66478  | 0       |
| Cysteine and methionine metabolism         | 56       | 0,11633  | 1    | 0,11113    | 2,1971  | 1           | 0,68386  | 0,00735 |
| Arginine and proline metabolism            | 77       | 0,15995  | 1    | 0,15016    | 1,8961  | 1           | 0,85803  | 0       |

**Supplementary Figure 10.** Metabolic routes altered in an opposite way by AuChi and AuCeO<sub>2</sub> particles.

**Supplementary Table 1.** Normalized concentration values of selected metabolites after 24 hours of treatment. P-values were obtained by the Student's t-test.

|                      | Time (h)     |        | 24      |         | 24     |       | 24    |         | 24     |        | 24 |  |
|----------------------|--------------|--------|---------|---------|--------|-------|-------|---------|--------|--------|----|--|
|                      | Nanomaterial |        | Control | Control | AuChi  | AuChi | AuChi | AuCeO2  | AuCeO2 | AuCeO2 | 24 |  |
| metabolite           | region (ppm) |        | mean    | SEM     | mean   | SEM   | P     | mean    | SEM    | P      |    |  |
| 3-hydroxyisovalerate | 1,247        | 1,2719 | 43,792  | 5,738   | 40,774 | 5,785 | 0,716 | 59,060  | 8,042  | 0,142  |    |  |
| acetate              | 1,91         | 1,93   | 8,473   | 0,692   | 8,267  | 0,665 | 0,833 | 11,912  | 0,862  | 0,007  |    |  |
| ADP/ATP              | 8,53         | 8,545  | 1,882   | 0,162   | 1,622  | 0,125 | 0,223 | 1,934   | 0,210  | 0,845  |    |  |
| alanine              | 1,47         | 1,51   | 14,499  | 0,865   | 13,518 | 0,714 | 0,395 | 15,777  | 1,319  | 0,430  |    |  |
| aspartate            | 2,79         | 2,84   | 3,717   | 0,346   | 3,554  | 0,326 | 0,737 | 4,018   | 0,368  | 0,559  |    |  |
| ATP                  | 4,39         | 4,43   | 5,617   | 0,491   | 5,789  | 0,539 | 0,817 | 0,838   | 4,158  | 0,270  |    |  |
| creatine/phocrea     | 3,0347       | 3,053  | 6,376   | 0,909   | 6,442  | 0,482 | 0,949 | 3,907   | 0,256  | 0,019  |    |  |
| formate              | 8,45         | 8,47   | 2,397   | 0,223   | 2,222  | 0,225 | 0,589 | 3,367   | 0,361  | 0,037  |    |  |
| fumarate             | 6,51         | 6,53   | 0,760   | 0,152   | 0,645  | 0,126 | 0,570 | 1,023   | 0,241  | 0,369  |    |  |
| glutamate            | 2,33         | 2,38   | 16,956  | 1,088   | 18,011 | 1,112 | 0,508 | 15,833  | 1,038  | 0,466  |    |  |
| glutamine            | 2,44         | 2,48   | 6,942   | 0,750   | 7,272  | 1,046 | 0,801 | 6,907   | 0,431  | 0,968  |    |  |
| glycerol             | 3,566        | 3,5711 | 0,798   | 0,068   | 0,846  | 0,107 | 0,709 | 1,571   | 0,533  | 0,169  |    |  |
| glycerol derivative  | 3,46         | 3,49   | 5,440   | 0,763   | 5,189  | 1,043 | 0,848 | 6,074   | 0,986  | 0,618  |    |  |
| glycine              | 3,5508       | 3,566  | 5,511   | 0,341   | 5,667  | 0,308 | 0,738 | 5,642   | 0,522  | 0,836  |    |  |
| GSSG                 | 3,295        | 3,3084 | 1,140   | 0,080   | 1,313  | 0,171 | 0,374 | 1,432   | 0,205  | 0,203  |    |  |
| histidine            | 7,08         | 7,09   | 0,480   | 0,058   | 0,429  | 0,054 | 0,533 | 0,677   | 0,137  | 0,205  |    |  |
| isoleucine           | 1,01         | 1,03   | 2,953   | 0,268   | 3,417  | 0,400 | 0,349 | 4,292   | 0,435  | 0,018  |    |  |
| lactate              | 1,31         | 1,37   | 79,900  | 8,651   | 77,429 | 9,282 | 0,848 | 109,693 | 14,925 | 0,103  |    |  |
| methionine           | 2,017        | 2,027  | 2,768   | 0,126   | 2,554  | 0,107 | 0,216 | 2,684   | 0,233  | 0,757  |    |  |
| NAD                  | 8,82         | 8,86   | 2,606   | 0,316   | 2,357  | 0,243 | 0,541 | 3,335   | 0,559  | 0,273  |    |  |
| phenylalanine        | 7,3          | 7,45   | 11,584  | 1,274   | 10,969 | 1,046 | 0,714 | 15,630  | 1,619  | 0,067  |    |  |
| phosphocholine       | 4,15         | 4,19   | 20,037  | 2,848   | 24,396 | 3,138 | 0,319 | 11,863  | 1,520  | 0,022  |    |  |
| pyruvate             | 2,38         | 2,4    | 5,125   | 0,375   | 5,280  | 0,443 | 0,793 | 6,798   | 0,497  | 0,016  |    |  |
| succinate            | 2,4          | 2,414  | 4,272   | 0,291   | 4,286  | 0,501 | 0,981 | 4,828   | 0,337  | 0,230  |    |  |
| taurine              | 3,407        | 3,445  | 6,485   | 0,449   | 6,632  | 0,890 | 0,885 | 6,071   | 0,839  | 0,669  |    |  |
| UDP der              | 4,36         | 4,39   | 6,253   | 0,577   | 6,370  | 0,336 | 0,863 | 3,635   | 2,161  | 0,259  |    |  |
| UDP-NAG              | 5,5          | 5,54   | 1,466   | 0,180   | 0,982  | 0,236 | 0,122 | 1,977   | 0,406  | 0,267  |    |  |
| valine               | 1,04         | 1,06   | 4,282   | 0,394   | 4,889  | 0,521 | 0,367 | 6,024   | 0,589  | 0,026  |    |  |

**Supplementary Table 2.** Normalized concentration values of selected metabolites after 48 hours of treatment. P-values were obtained by the Student's t-test.

|                      | Time (h)     |        | 48      |         | 48      |        | 48    |         | 48     |        | 48 |  |
|----------------------|--------------|--------|---------|---------|---------|--------|-------|---------|--------|--------|----|--|
|                      | Nanomaterial |        | Control | Control | AuChi   | AuChi  | AuChi | AuCeO2  | AuCeO2 | AuCeO2 | 48 |  |
| metabolite           | region (ppm) |        | mean    | SEM     | mean    | SEM    | P     | mean    | SEM    | P      |    |  |
| 3-hydroxyisovalerate | 1,247        | 1,2719 | 20,496  | 2,299   | 37,770  | 5,155  | 0,007 | 24,948  | 2,426  | 0,201  |    |  |
| acetate              | 1,91         | 1,93   | 5,991   | 0,349   | 8,780   | 0,913  | 0,012 | 6,632   | 0,472  | 0,292  |    |  |
| ADP/ATP              | 8,53         | 8,545  | 2,435   | 0,305   | 1,826   | 0,311  | 0,181 | 2,361   | 0,218  | 0,846  |    |  |
| alanine              | 1,47         | 1,51   | 15,965  | 0,515   | 13,806  | 0,542  | 0,011 | 13,899  | 0,530  | 0,013  |    |  |
| aspartate            | 2,79         | 2,84   | 2,379   | 0,228   | 3,117   | 0,362  | 0,104 | 2,464   | 0,222  | 0,793  |    |  |
| ATP                  | 4,39         | 4,43   | 8,125   | 0,736   | 5,957   | 1,094  | 0,120 | 7,601   | 0,664  | 0,604  |    |  |
| creatine/phocrea     | 3,0347       | 3,053  | 12,934  | 1,452   | 6,658   | 1,889  | 0,018 | 8,582   | 0,717  | 0,016  |    |  |
| formate              | 8,45         | 8,47   | 1,653   | 0,166   | 2,764   | 0,396  | 0,020 | 1,944   | 0,201  | 0,280  |    |  |
| fumarate             | 6,51         | 6,53   | 0,573   | 0,100   | 0,685   | 0,115  | 0,475 | 0,550   | 0,102  | 0,872  |    |  |
| glutamate            | 2,33         | 2,38   | 16,111  | 0,890   | 15,664  | 0,973  | 0,739 | 12,545  | 0,337  | 0,002  |    |  |
| glutamine            | 2,44         | 2,48   | 3,275   | 0,250   | 4,445   | 0,427  | 0,031 | 3,465   | 0,319  | 0,644  |    |  |
| glycerol             | 3,566        | 3,5711 | 1,315   | 0,096   | 1,482   | 0,273  | 0,571 | 1,718   | 0,232  | 0,128  |    |  |
| glycerol derivative  | 3,46         | 3,49   | 4,593   | 0,641   | 4,820   | 0,843  | 0,833 | 6,885   | 1,357  | 0,146  |    |  |
| glycine              | 3,5508       | 3,566  | 8,146   | 0,395   | 6,625   | 0,279  | 0,006 | 7,333   | 0,303  | 0,122  |    |  |
| GSSG                 | 3,295        | 3,3084 | 1,154   | 0,054   | 1,693   | 0,140  | 0,002 | 1,121   | 0,069  | 0,710  |    |  |
| histidine            | 7,08         | 7,09   | 0,368   | 0,043   | 0,471   | 0,067  | 0,214 | 0,392   | 0,042  | 0,688  |    |  |
| isoleucine           | 1,01         | 1,03   | 2,330   | 0,236   | 2,888   | 0,311  | 0,172 | 2,171   | 0,155  | 0,580  |    |  |
| lactate              | 1,31         | 1,37   | 161,599 | 6,528   | 116,774 | 14,096 | 0,011 | 203,415 | 10,241 | 0,003  |    |  |
| methionine           | 2,017        | 2,027  | 3,779   | 0,254   | 2,762   | 0,360  | 0,035 | 3,138   | 0,167  | 0,051  |    |  |
| NAD                  | 8,82         | 8,86   | 2,118   | 0,144   | 2,624   | 0,310  | 0,159 | 2,351   | 0,213  | 0,378  |    |  |
| phenylalanine        | 7,3          | 7,45   | 8,690   | 0,794   | 12,327  | 1,195  | 0,022 | 9,384   | 0,835  | 0,555  |    |  |
| phosphocholine       | 4,15         | 4,19   | 18,547  | 1,692   | 21,426  | 2,668  | 0,376 | 14,758  | 1,347  | 0,099  |    |  |
| pyruvate             | 2,38         | 2,4    | 4,233   | 0,298   | 6,223   | 0,650  | 0,013 | 4,689   | 0,390  | 0,366  |    |  |
| succinate            | 2,4          | 2,414  | 6,281   | 0,244   | 5,170   | 0,332  | 0,016 | 6,395   | 0,253  | 0,749  |    |  |
| taurine              | 3,407        | 3,445  | 6,369   | 0,515   | 4,911   | 0,358  | 0,034 | 4,587   | 0,185  | 0,005  |    |  |
| UDP der              | 4,36         | 4,39   | 13,729  | 0,935   | 10,651  | 1,322  | 0,076 | 13,023  | 0,982  | 0,610  |    |  |
| UDP-NAG              | 5,5          | 5,54   | 2,768   | 0,376   | 2,357   | 0,376  | 0,451 | 2,813   | 0,409  | 0,937  |    |  |
| valine               | 1,04         | 1,06   | 3,690   | 0,330   | 4,625   | 0,360  | 0,074 | 3,343   | 0,192  | 0,376  |    |  |

**Supplementary Table 3.** Normalized concentration values of selected metabolites after 72 hours of treatment. P-values were obtained by the Student's t-test.

|                      | c            |        | 72      |        | 72      |        | 72    |         | 72     |       | 72     |     |
|----------------------|--------------|--------|---------|--------|---------|--------|-------|---------|--------|-------|--------|-----|
|                      | Nanomaterial |        | Control |        | AuChi   |        | AuChi |         | AuCeO2 |       | AuCeO2 |     |
| metabolite           | region (ppm) |        | mean    | SEM    | mean    | SEM    | P     | mean    | SEM    | P     | mean   | SEM |
| 3-hydroxyisovalerate | 1,247        | 1,2719 | 24,012  | 1,291  | 24,463  | 3,677  | 0,909 | 40,862  | 3,113  | 0,000 |        |     |
| acetate              | 1,91         | 1,93   | 6,498   | 0,222  | 5,835   | 0,789  | 0,431 | 9,653   | 0,801  | 0,002 |        |     |
| ADP/ATP              | 8,53         | 8,545  | 2,309   | 0,227  | 1,911   | 0,322  | 0,327 | 1,715   | 0,176  | 0,055 |        |     |
| alanine              | 1,47         | 1,51   | 16,812  | 0,305  | 14,378  | 1,865  | 0,216 | 15,784  | 0,969  | 0,327 |        |     |
| aspartate            | 2,79         | 2,84   | 2,548   | 0,096  | 2,132   | 0,296  | 0,199 | 3,328   | 0,279  | 0,018 |        |     |
| ATP                  | 4,39         | 4,43   | 9,273   | 0,481  | 7,621   | 1,128  | 0,197 | 5,690   | 0,352  | 0,000 |        |     |
| creatine/phocrea     | 3,0347       | 3,053  | 13,233  | 0,481  | 11,700  | 1,508  | 0,347 | 6,307   | 0,305  | 0,000 |        |     |
| formate              | 8,45         | 8,47   | 1,650   | 0,074  | 1,437   | 0,209  | 0,352 | 2,647   | 0,279  | 0,003 |        |     |
| fumarate             | 6,51         | 6,53   | 0,687   | 0,048  | 0,519   | 0,087  | 0,112 | 0,874   | 0,065  | 0,035 |        |     |
| glutamate            | 2,33         | 2,38   | 9,995   | 0,963  | 7,635   | 1,092  | 0,125 | 10,216  | 0,781  | 0,861 |        |     |
| glutamine            | 2,44         | 2,48   | 3,594   | 0,124  | 2,973   | 0,439  | 0,192 | 5,089   | 0,593  | 0,025 |        |     |
| glycerol             | 3,566        | 3,5711 | 1,397   | 0,245  | 0,987   | 0,146  | 0,171 | 1,464   | 0,149  | 0,818 |        |     |
| glycerol derivative  | 3,46         | 3,49   | 5,044   | 0,422  | 4,609   | 0,629  | 0,574 | 6,714   | 0,365  | 0,009 |        |     |
| glycine              | 3,5508       | 3,566  | 8,370   | 0,201  | 7,214   | 0,928  | 0,241 | 6,914   | 0,289  | 0,001 |        |     |
| GSSG                 | 3,295        | 3,3084 | 1,125   | 0,083  | 0,900   | 0,127  | 0,156 | 1,180   | 0,071  | 0,623 |        |     |
| histidine            | 7,08         | 7,09   | 0,449   | 0,018  | 0,422   | 0,060  | 0,666 | 0,605   | 0,031  | 0,000 |        |     |
| isoleucine           | 1,01         | 1,03   | 3,068   | 0,177  | 2,675   | 0,345  | 0,326 | 3,059   | 0,113  | 0,968 |        |     |
| lactate              | 1,31         | 1,37   | 207,204 | 11,667 | 182,754 | 24,312 | 0,378 | 219,994 | 19,509 | 0,581 |        |     |
| methionine           | 2,017        | 2,027  | 3,396   | 0,146  | 3,233   | 0,382  | 0,695 | 2,722   | 0,114  | 0,002 |        |     |
| NAD                  | 8,82         | 8,86   | 2,360   | 0,059  | 2,129   | 0,294  | 0,454 | 2,916   | 0,239  | 0,038 |        |     |
| phenylalanine        | 7,3          | 7,45   | 10,175  | 0,347  | 9,119   | 1,257  | 0,430 | 12,849  | 1,061  | 0,029 |        |     |
| phosphocholine       | 4,15         | 4,19   | 7,842   | 0,310  | 6,620   | 0,899  | 0,217 | 7,043   | 0,622  | 0,267 |        |     |
| pyruvate             | 2,38         | 2,4    | 3,821   | 0,264  | 3,242   | 0,508  | 0,327 | 5,734   | 0,796  | 0,037 |        |     |
| succinate            | 2,4          | 2,414  | 5,568   | 0,122  | 4,308   | 0,557  | 0,042 | 5,062   | 0,197  | 0,045 |        |     |
| taurine              | 3,407        | 3,445  | 6,936   | 0,150  | 6,536   | 0,848  | 0,649 | 4,942   | 0,121  | 0,000 |        |     |
| UDP der              | 4,36         | 4,39   | 18,774  | 0,673  | 15,691  | 2,055  | 0,173 | 11,341  | 0,699  | 0,000 |        |     |
| UDP-NAG              | 5,5          | 5,54   | 5,231   | 0,139  | 3,594   | 1,114  | 0,164 | 3,468   | 0,164  | 0,000 |        |     |
| valine               | 1,04         | 1,06   | 4,501   | 0,277  | 4,005   | 0,524  | 0,415 | 4,569   | 0,232  | 0,854 |        |     |