SUPPLEMENTARY DATA

Two drugs used together is pharmacodynamically synergistic, additive or antagonistic if the therapeutic effect is greater than, equal to, or less than the summed effects of the partner drugs [47]. Drug combinations may also produce pharmacokinetically potentiative or reductive effects such that the therapeutic activity of one drug is enhanced or reduced by another drug [47]. Another type of drug combination is a coalistic combination, in which all of the drugs involved are inactive individually but are active in combination [48]. In this study, we only consider three pharmacodynamical types of drug combinations: synergistic, additive and antagonistic effects.

We define the DEGs between the non-responders and responders of patients treated with drug A and B as CRGs for the combination chemotherapy, denoted as CRG<sub>AB</sub>. The DEGs between the non-responders and responders of patients treated with drug A or B alone were defined as CRGs for drug A or CRGs for drug B, denoted as CRG<sub>A</sub> or CRG<sub>B</sub>, respectively. If CRG<sub>A</sub> and CRG<sub>B</sub> have overlaps, then we define each of the overlapped genes as a synergistic or antagonistic gene if it has the same or opposite deregulation directions (up-regulation or down-regulation) in the non-responders compared with the responders) in CRG<sub>A</sub> and CRG<sub>B</sub>. Then, we can prove the following conclusions:

1. If a CRG<sub>A</sub> (CRG<sub>B</sub>) is not a CRG<sub>AB</sub> (CRG<sub>AB</sub>), then it is statistically expected to be detected as a CRG<sub>AB</sub> with the same deregulation direction in non-responders compared with responders.

2. For a synergistic gene included in both CRG<sub>A</sub> and CRG<sub>B</sub>, it is expected to be included in CRG<sub>AB</sub> with the same deregulation direction.

3. For an antagonistic gene, it may or may not be detected as a CRG<sub>AB</sub>. If it is also detected as a CRG<sub>AB</sub>, then its deregulation direction could be inconsistent with CRG<sub>A</sub> or CRG<sub>B</sub>.

4. If the frequency of antagonistic genes in CRG<sub>A</sub> or CRG<sub>B</sub> is small, then the consistence score between the CRG<sub>A</sub> or CRG<sub>B</sub> and CRG<sub>AB</sub> should be significant.

5. The same conclusions can be proven for combination chemotherapy with more than two drugs.

Under the same assumption that the frequency of antagonistic genes is small, we can prove the following conclusion:

6. If two different regimens share one or several drugs, then the overlaps of CRGs for the two different regimens should be the CRGs for the shared drug(s).

Proof. We assume that the non-responders are resistant to all the drugs used together (subtype0) and the responders have three subtypes: sensitive to drug B only(subtype1), sensitive to drug A only(subtype2), and sensitive to both A and B(subtype3). For any of CRG<sub>A</sub>, denoted as g<sub>A</sub>, we suppose that expectation of its expression value in subtype <i>i</i> is μ<sub><i>g</sub>A,i</sub> (i = 0,1,2,3). The frequency of subtypes in the non-responder and responder groups for combination chemotherapy is \( f(i=0,1,2,3, f_1+f_2+f_3 = 1) \).

The four kinds of sample subtypes were displayed in the following table:

| Drug A | Drug B | μ<sub>g</sub><sub>A</sub> | f<sub>i</sub> |
|--------|--------|-----------------|-------|
| Non-responder | 1 | 1 | μ<sub>g</sub>00 | f<sub>0</sub> |
| | 0 | 0 | μ<sub>g</sub>01 + f<sub>1</sub> |
| Responder | 0 | 1 | μ<sub>g</sub>12 | f<sub>2</sub> |
| | 0 | 0 | μ<sub>g</sub>13 | f<sub>3</sub> |

Note: 1(0): resistance(sensitive) to one drug;
μ<sub>g</sub>0: the expectation of expression value of g<sub>A</sub> in the non-responder and responder groups(=0,1,2,3);
f<sub>i</sub>: the frequency of subtypes in the non-responder and responder groups(=0,1,2,3).

According the table above, μ<sub>g</sub>00 - μ<sub>g</sub>01 and μ<sub>g</sub>10 - μ<sub>g</sub>12 both represent the difference of g<sub>A</sub> in the non-responders compared with the responders for drug A, we define

\[ \Delta_\text{A}(g_A) = μ_{g_A0} - μ_{g_A1} = μ_{g_A1} - μ_{g_A0} \]

Similarly,

\[ \Delta_\text{A}(g_A) = μ_{g_A0} - μ_{g_A1} = μ_{g_A1} - μ_{g_A0} \]

We further define Δ<sub>AB</sub>(g<sub>A</sub>) as the difference of g<sub>A</sub> in the non-responders compared with the responders for combination chemotherapy with drug A and drug B, then,

\[ ∴ μ_{g_{AB}} - μ_{g_{BA}} = μ_{g_{AB}} - μ_{g_{BA}} \]

\[ ∴ μ_{g_{AB}} = μ_{g_{BA}} + μ_{g_{AB}} - μ_{g_{AB}} \]

\[ ∴ f_1 + f_2 + f_3 = 1 \]

\[ Δ_\text{AB}(g_A) = μ_{g_{AB}} - (μ_{g_{AB}} + f_2μ_{g_{BA}} + f_3μ_{g_{BA}}) \]

= μ<sub>g</sub>00(f<sub>1</sub> + f<sub>2</sub> + f<sub>3</sub> - f<sub>1</sub>μ<sub>g</sub>00 + f<sub>2</sub>μ<sub>g</sub>00 + f<sub>3</sub>μ<sub>g</sub>00) - f<sub>3</sub>μ<sub>g</sub>00 - f<sub>2</sub>μ<sub>g</sub>00

= f<sub>1</sub>Δ<sub>A</sub>(g<sub>A</sub>) + f<sub>2</sub>Δ<sub>B</sub>(g<sub>A</sub>) + f<sub>3</sub>Δ<sub>B</sub>(g<sub>A</sub>)

= f<sub>1</sub>Δ<sub>A</sub>(g<sub>A</sub>) + f<sub>2</sub>Δ<sub>B</sub>(g<sub>A</sub>) + f<sub>3</sub>Δ<sub>B</sub>(g<sub>A</sub>)

= (1 - f<sub>1</sub>)Δ<sub>A</sub>(g<sub>A</sub>) + (1 - f<sub>2</sub>)Δ<sub>B</sub>(g<sub>A</sub>)

For Δ<sub>AB</sub>(g<sub>A</sub>) = (1 - f<sub>1</sub>)Δ<sub>A</sub>(g<sub>A</sub>) + (1 - f<sub>2</sub>)Δ<sub>B</sub>(g<sub>A</sub>) (0 ≤ f<sub>1</sub> ≤ 1, 0 ≤ f<sub>2</sub> ≤ 1)

we suppose Δ<sub>A</sub>(g<sub>A</sub>) > 0, which means g<sub>A</sub> is up-regulated in the non-responders compared with the responders for drug A.

1. if g<sub>A</sub> ∉ (CRG<sub>A</sub> ∩ CRG<sub>B</sub>) then Δ<sub>AB</sub>(g<sub>A</sub>) = 0, which means g<sub>A</sub> has no difference in the non-responders
compared with the responders for drug B and the two drugs act independently to each other. Thus
\( \Delta_{\text{A,B}}(g) = (1 - f_1)\Delta_{\text{A}}(g) \geq 0; \)

2. If \( g \in (\text{CRG}_A \cap \text{CRG}_B) \) and \( \Delta_{\text{A}}(g) > 0 \), which means \( g \) is a synergistic gene, then \( \Delta_{\text{A,B}}(g) = (1 - f_1)\Delta_{\text{A}}(g) + (1 - f_2)\Delta_{\text{B}}(g) \geq 0; \)

3. If \( g \in (\text{CRG}_A \cap \text{CRG}_B) \) and \( \Delta_{\text{B}}(g) < 0 \), which means \( g \) is an antagonistic gene,
\[
\text{Only when } \frac{-\Delta_{\text{B}}(g)}{\Delta_{\text{A}}(g)} < \frac{1 - f_1}{1 - f_1} = \frac{1 - f_1}{f_1 + f_2} < \frac{1 - f_2}{f_2} \text{ then,}
\]
\[
\Delta_{\text{A,B}}(g) < 0 \\
\therefore \Delta_{\text{A}}(g) > 0, \Delta_{\text{B}}(g) < 0
\]
\[
\therefore \frac{-\Delta_{\text{B}}(g)}{\Delta_{\text{A}}(g)} > 0
\]

Only when \( f_2 \) which represents the sample size of responders who are sensitive to drug A is small enough, then \( \Delta_{\text{A,B}}(g) < 0 \). In fact, accumulated empirical clinical experience showed that cytotoxic drugs given in combination was to achieve additive or synergistic effects [49].

Similarly, the same conclusions can be proven when \( g \) down-regulated in the non-responders compared with the responders for drug A. The mathematical derivations above can be summarized to the following derivations more concisely:

\( G \): the whole genes set.

\( \Delta_{\text{A}}(g) \): the expection difference of gene g between the sensitive and resistant samples of a drug X.

\( \text{CRG}_i = \{g \mid g \in G \land \Delta_{\text{A}}(g) \neq 0 \} \)

\( \text{CRG}_j = \{g \mid g \in G \land \Delta_{\text{B}}(g) \neq 0 \} \)

Let

\( \text{CRG}_{i,j} = \text{CRG}_i \cup \text{CRG}_j \)

\( \text{CRG} = (\text{CRG}_i - \text{CRG}_j) \cup (\text{CRG}_j - \text{CRG}_i) \cup (\text{CRG}_i \cap \text{CRG}_j) \)

no overlap
\[
\therefore \forall g \in \text{CRG}_i \rightarrow \Delta_{\text{A}}(g) = 0
\]

\( \therefore \forall g \in (\text{CRG}_i - \text{CRG}_j) \rightarrow \Delta_{\text{B}}(g) \neq 0 \)

Similarly,

\( \forall g \in (\text{CRG}_j - \text{CRG}_i) \rightarrow \Delta_{\text{A}}(g) = 0 \)
\[
\therefore \forall g \in (\text{CRG}_j - \text{CRG}_i) \rightarrow \Delta_{\text{B}}(g) \neq 0 \text{ or } f_i \leq 1
\]
\[
\therefore \Delta_{\text{B}}(g) = \text{CRG}_j - \text{CRG}_i \subseteq \text{CRG}
\]

Similarly,

\( \text{CRG}_i - \text{CRG}_j \subseteq \text{CRG} \)

synergistic gene
\[
\exists g \in (\text{CRG}_i \cap \text{CRG}_j) \land (\Delta_{\text{A}}(g) \Delta_{\text{B}}(g) > 0) \rightarrow \Delta_{\text{A}} = (1 - f_1)\Delta_{\text{A}}(g) + (1 - f_2)\Delta_{\text{B}}(g) \neq 0
\]
\[
\{g \mid g \in (\text{CRG}_i \cap \text{CRG}_j) \land (\Delta_{\text{A}}(g) \Delta_{\text{B}}(g) > 0) \subseteq \text{CRG}
\]

antagonistic gene

1. confusing direction
\[
\text{for } \{g \mid g \in (\text{CRG}_i \cap \text{CRG}_j) \land (\Delta_{\text{A}}(g) \Delta_{\text{B}}(g) < 0) \} \land \Delta_{\text{A}} \neq 0
\]

Above all, we believe that \( \text{CRG} \subseteq \text{CRG}_{i,j} \) and most genes in the two gene sets have the same deregulation directions.

End

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## Supplementary Table S1: The consistency scores of the top-ranked 1500 BD and IP\textsubscript{6}, IP\textsubscript{12}, IP\textsubscript{24} genes detected from HCT1116 cell line

| Dataset        | Cell line | Drug   | Method | IP  | Overlapped DEG | Consistent DEG(%) | Binominal P-value |
|----------------|-----------|--------|--------|-----|----------------|-------------------|-------------------|
| E-MEXP-390     | HCT116    | 5-FU   | FC     | IP\textsubscript{6} | 510             | 98.24             | <1.11E-16         |
|                |           |        |        | AD   | 987             | 95.04             | <1.11E-16         |
|                |           |        | FC     | IP\textsubscript{12} | 673             | 98.37             | <1.11E-16         |
|                |           |        |        | AD   | 990             | 93.33             | <1.11E-16         |
|                |           |        | FC     | IP\textsubscript{24} | 523             | 98.28             | <1.11E-16         |
|                |           |        |        | AD   | 922             | 88.61             | <1.11E-16         |
| E-MEXP-390     | HCT116    | L-OHP  | FC     | IP\textsubscript{6} | 902             | 100.00            | <1.11E-16         |
|                |           |        |        | AD   | 1178            | 98.90             | <1.11E-16         |
|                |           |        | FC     | IP\textsubscript{12} | 885             | 100.00            | <1.11E-16         |
|                |           |        |        | AD   | 1107            | 98.84             | <1.11E-16         |
|                |           |        | FC     | IP\textsubscript{24} | 672             | 99.55             | <1.11E-16         |
|                |           |        |        | AD   | 1092            | 93.40             | <1.11E-16         |
| E-MEXP-1691    | HCT116    | 5-FU   | FC     | IP\textsubscript{24} | 853             | 99.53             | <1.11E-16         |
|                |           |        |        | AD   | 1184            | 97.13             | <1.11E-16         |
| E-MEXP-1691    | HCT116    | SN38   | FC     | IP\textsubscript{24} | 885             | 98.76             | <1.11E-16         |
|                |           |        |        | AD   | 1171            | 96.16             | <1.11E-16         |
| E-MEXP-1171    | HCT116    | SN38   | FC     | IP\textsubscript{6} | 553             | 98.69             | <1.11E-16         |
|                |           |        |        | AD   | 912             | 83.23             | <1.11E-16         |
|                |           |        | FC     | IP\textsubscript{12} | 445             | 94.83             | <1.11E-16         |
|                |           |        |        | AD   | 933             | 86.28             | <1.11E-16         |
|                |           |        | FC     | IP\textsubscript{24} | 439             | 92.48             | <1.11E-16         |
|                |           |        |        | AD   | 951             | 90.12             | <1.11E-16         |
Supplementary Table S2: The consistency scores of the top-ranked 3000 (top-ranked 1500) BD genes and IP<sub>24</sub> genes detected from other cell line datasets

| Dataset  | Cell line          | Drug | Method | Overlapped DEG<sup>a</sup> | Consistent DEG<sup>b</sup>(%) | Binominal P-value<sup>c</sup> |
|----------|--------------------|------|--------|---------------------------|-------------------------------|-------------------------------|
| GSE3926  | HT29 (colon)       | Doxo | FC     | 1773 (691)                 | 88.16 (91.03)                 | <4.20E-09 (<4.20E-09)         |
|          |                    |      | AD     | 1913 (877)                 | 80.55 (83.35)                 | <4.20E-09 (<4.20E-09)         |
| GSE3926  | MCF-7 (breast)     | Doxo | FC     | 1640 (673)                 | 86.10 (93.16)                 | <4.20E-09 (<4.20E-09)         |
|          |                    |      | AD     | 1996 (913)                 | 84.62 (86.86)                 | <4.20E-09 (<4.20E-09)         |
| GSE3926  | EPP85-181P (pancreatic) | Doxo | FC    | 1464 (626)                 | 86.07 (92.49)                 | <4.20E-09 (<4.20E-09)         |
|          |                    |      | AD     | 2014 (921)                 | 81.58 (79.80)                 | <4.20E-09 (<4.20E-09)         |
| GSE3926  | EPG85-257P (gastric) | Doxo | FC    | 1463 (642)                 | 85.92 (91.74)                 | <4.20E-09 (<4.20E-09)         |
|          |                    |      | AD     | 2007 (875)                 | 72.35 (74.51)                 | <4.20E-09 (<4.20E-09)         |

<sup>a</sup>The number of BD genes overlapped with IP<sub>24</sub> genes;
<sup>b</sup>The consistency score of BD genes and IP<sub>24</sub> genes;
<sup>c</sup>The binominal distribution P-value.
Supplementary Table S3: The 315 CRG_{FUL-OHP} detected from the GSE19860, GSE28702 and E-MEXP-3368 datasets

| Geneid | Gene Symbol | Direction |
|--------|-------------|-----------|
| 9      | NAT1        | up        |
| 26     | ABP1        | up        |
| 72     | ACTG2       | up        |
| 136    | ADORA2B     | up        |
| 283    | ANG         | up        |
| 339    | APOBEC1     | up        |
| 430    | ASCL2       | up        |
| 688    | KLF5        | up        |
| 701    | BUB1B       | up        |
| 891    | CCNB1       | up        |
| 990    | CDC6        | up        |
| 1015   | CDH17       | up        |
| 1033   | CDKN3       | up        |
| 1113   | CHGA        | up        |
| 1179   | CLCA1       | up        |
| 1363   | CPE         | up        |
| 1365   | CLDN3       | up        |
| 1366   | CLDN7       | up        |
| 1644   | DDC         | up        |
| 1690   | COCH        | up        |
| 1836   | SLC26A2     | up        |
| 2049   | EPHB3       | up        |
| 2150   | F2RL1       | up        |
| 2295   | FOXF2       | up        |
| 2330   | FMO5        | up        |
| 2487   | FRZB        | up        |
| 2494   | NR5A2       | up        |
| 2524   | FUT2        | up        |
| 2525   | FUT3        | up        |
| 2526   | FUT4        | up        |
| 2641   | GCG         | up        |
| 2762   | GMDS        | up        |
| 2921   | CXCL3       | up        |
| 2980   | GUCA2A      | up        |
| 3115   | HLA-DPB1    | up        |

(Continued)
| Geneid | Gene Symbol | Direction |
|--------|-------------|-----------|
| 3158   | HMGCS2      | up        |
| 3171   | FOXA3       | up        |
| 3174   | HNF4G       | up        |
| 3207   | HOXA11      | up        |
| 3209   | HOXA13      | up        |
| 3306   | HSPA2       | up        |
| 3574   | IL7         | up        |
| 3613   | IMPA2       | up        |
| 3832   | KIF11       | up        |
| 3957   | LGALS2      | up        |
| 3960   | LGALS4      | up        |
| 4013   | VWA5A       | up        |
| 4128   | MAOA        | up        |
| 4171   | MCM2        | up        |
| 4246   | SCGB2A1     | up        |
| 4306   | NR3C2       | up        |
| 4314   | MMP3        | up        |
| 4499   | MT1M        | up        |
| 4583   | MUC2        | up        |
| 4585   | MUC4        | up        |
| 4602   | MYB         | up        |
| 4640   | MYO1A       | up        |
| 4751   | NEK2        | up        |
| 4982   | TNFRSF11B   | up        |
| 4998   | ORC1        | up        |
| 5105   | PCK1        | up        |
| 5122   | PCSK1       | up        |
| 5205   | ATP8B1      | up        |
| 5284   | PIGR        | up        |
| 5318   | PKP2        | up        |
| 5320   | PLA2G2A     | up        |
| 5325   | PLAGL1      | up        |
| 5357   | PLS1        | up        |
| 5468   | PPARG       | up        |
| 5557   | PRIM1       | up        |
| 5789   | PTPRD       | up        |

(Continued)
| Geneid | Gene Symbol | Direction |
|--------|-------------|-----------|
| 5918   | RARRES1     | up        |
| 5984   | RFC4        | up        |
| 5985   | RFC5        | up        |
| 6038   | RNASE4      | up        |
| 6491   | STIL        | up        |
| 6549   | SLC9A2      | up        |
| 6596   | HLTF        | up        |
| 6690   | SPINK1      | up        |
| 6717   | SRI         | up        |
| 6920   | TCEA3       | up        |
| 7033   | TFF3        | up        |
| 7098   | TLR3        | up        |
| 7153   | TOP2A       | up        |
| 7263   | TST         | up        |
| 7298   | TTK         | up        |
| 7298   | TYMS        | up        |
| 7368   | UGT8        | up        |
| 7374   | UNG         | up        |
| 7398   | USP1        | up        |
| 7443   | VRK1        | up        |
| 7504   | XK          | up        |
| 7850   | IL1R2       | up        |
| 8618   | CADPS       | up        |
| 8702   | B4GALT4     | up        |
| 8792   | TNFRSF11A   | up        |
| 8857   | FCGBP       | up        |
| 9037   | SEMA5A      | up        |
| 9055   | PRC1        | up        |
| 9134   | CCNE2       | up        |
| 9166   | EBAG9       | up        |
| 9245   | GCNT3       | up        |
| 9314   | KLF4        | up        |
| 9582   | APOBEC3B    | up        |
| 9787   | DLGAP5      | up        |
| 9928   | KIF14       | up        |
| Geneid | Gene Symbol | Direction |
|--------|-------------|-----------|
| 9982   | FGFBP1      | up        |
| 10008  | KCNE3       | up        |
| 10020  | GNE         | up        |
| 10103  | TSPAN1      | up        |
| 10112  | KIF20A      | up        |
| 10158  | PDZK1IP1    | up        |
| 10189  | ALYREF      | up        |
| 10223  | GPA33       | up        |
| 10403  | NDC80       | up        |
| 10406  | WFDC2       | up        |
| 10418  | SPON1       | up        |
| 10481  | HOXB13      | up        |
| 10551  | AGR2        | up        |
| 10559  | SLC35A1     | up        |
| 10605  | PAIP1       | up        |
| 10615  | SPAG5       | up        |
| 10753  | CAPN9       | up        |
| 10903  | MTMR11      | up        |
| 11004  | KIF2C       | up        |
| 11005  | SPINK5      | up        |
| 11130  | ZWINT       | up        |
| 23171  | GPD1L       | up        |
| 23321  | TRIM2       | up        |
| 23443  | SLC35A3     | up        |
| 23584  | VSIG2       | up        |
| 25994  | HIGD1A      | up        |
| 26018  | LRIG1       | up        |
| 26060  | APPL1       | up        |
| 26298  | EHF         | up        |
| 26996  | GPR160      | up        |
| 27035  | NOX1        | up        |
| 27075  | TSPAN13     | up        |
| 27283  | TINAG       | up        |
| 27284  | SULT1B1     | up        |
| 27290  | SPINK4      | up        |
| 29091  | STXBPH6     | up        |

(Continued)
| Geneid  | Gene Symbol | Directiona |
|---------|-------------|------------|
| 29968   | PSAT1       | up         |
| 50853   | VILL        | up         |
| 51000   | SLC35B3     | up         |
| 51195   | RAPGEFL1    | up         |
| 51203   | NUSAP1      | up         |
| 51514   | DTL         | up         |
| 51567   | TDP2        | up         |
| 51703   | ACSL5       | up         |
| 51809   | GALNT7      | up         |
| 54474   | KRT20       | up         |
| 54546   | RNF186      | up         |
| 54596   | L1TD1       | up         |
| 54827   | FAM55D      | up         |
| 54836   | BSPRY       | up         |
| 54843   | SYT2       | up         |
| 54845   | ESRP1       | up         |
| 54847   | SIDT1       | up         |
| 54860   | MS4A12      | up         |
| 54866   | PPP1R14D    | up         |
| 54933   | RHBDL2      | up         |
| 55040   | EPN3        | up         |
| 55179   | FAIM        | up         |
| 55204   | GOLPH3L     | up         |
| 55286   | C4orf19     | up         |
| 55502   | HES6        | up         |
| 55600   | ITLN1       | up         |
| 55635   | DEPDC1      | up         |
| 55711   | FAR2        | up         |
| 55769   | ZNF83       | up         |
| 55808   | ST6GALNAC1  | up         |
| 55930   | MYO5C       | up         |
| 56267   | CCBL2       | up         |
| 56925   | LXN         | up         |
| 56987   | BBX         | up         |
| 56992   | KIF15       | up         |
| 57111   | RAB25       | up         |

(Continued)
| Geneid  | Gene Symbol | Direction |
|---------|-------------|-----------|
| 57126   | CD177       | up        |
| 57216   | VANGL2      | up        |
| 57405   | SPC25       | up        |
| 57475   | PLEKHH1     | up        |
| 57482   | KIAA1211    | up        |
| 57535   | KIAA1324    | up        |
| 57552   | NCEH1       | up        |
| 57643   | ZSWIM5      | up        |
| 63928   | CHP2        | up        |
| 64073   | C19orf33    | up        |
| 64105   | CENPK       | up        |
| 64417   | C5orf28     | up        |
| 64426   | SUDS3       | up        |
| 64922   | LRRC19      | up        |
| 79083   | MLPH        | up        |
| 79170   | PRR15L      | up        |
| 79682   | MLF11P      | up        |
| 79730   | NSUN7       | up        |
| 79733   | E2F8        | up        |
| 79782   | LRRC31      | up        |
| 79789   | CLMN        | up        |
| 80117   | ARL14       | up        |
| 80150   | ASRGL1      | up        |
| 80157   | CWH43       | up        |
| 80736   | SLC44A4     | up        |
| 81575   | APOLD1      | up        |
| 81618   | ITM2C       | up        |
| 83661   | MS4A8B      | up        |
| 83699   | SH3BGRL2    | up        |
| 84057   | MND1        | up        |
| 84152   | PPP1R1B     | up        |
| 84302   | TMEM246     | up        |
| 84419   | C15orf48    | up        |
| 84708   | LNX1        | up        |
| 84842   | HPDL        | up        |
| 85315   | PAQR8       | up        |
| 90333   | ZNF468      | up        |

(Continued)
| Geneid  | Gene Symbol | Direction |
|---------|-------------|-----------|
| 91392   | ZNF502      | up        |
| 112609  | MRAP2       | up        |
| 113802  | HENMT1      | up        |
| 114907  | FBXO32      | up        |
| 116832  | RPL39L      | up        |
| 120400  | FAM55A      | up        |
| 124975  | GGT6        | up        |
| 131076  | CCDC58      | up        |
| 131177  | FAM3D       | up        |
| 138065  | RNF183      | up        |
| 139886  | SPIN4       | up        |
| 145376  | PPP1R36     | up        |
| 148170  | CDC42EP5    | up        |
| 148418  | SAMD13      | up        |
| 149175  | MANEAL      | up        |
| 150209  | AIFM3       | up        |
| 151246  | SGOL2       | up        |
| 151473  | SLC16A14    | up        |
| 151827  | LRRC34      | up        |
| 152100  | CMC1        | up        |
| 155465  | AGR3        | up        |
| 171546  | SPTSSA      | up        |
| 192134  | B3GNT6      | up        |
| 200958  | MUC20       | up        |
| 220963  | SLC16A9     | up        |
| 221061  | FAM171A1    | up        |
| 221443  | C6orf130    | up        |
| 222171  | PRR15       | up        |
| 253012  | HEPACAM2    | up        |
| 255738  | PCSK9       | up        |
| 282809  | POC1B       | up        |
| 285704  | RGMB        | up        |
| 340277  | FAM221A     | up        |
| 401546  | C9orf152    | up        |
| 653808  | ZG16        | up        |
| 100133941 | CD24  | up        |

(Continued)
| Geneid | Gene Symbol | Direction |
|--------|-------------|-----------|
| 341    | APOC1       | down      |
| 684    | BST2        | down      |
| 712    | C1QA        | down      |
| 952    | CD38        | down      |
| 978    | CDA         | down      |
| 1109   | AKR1C4      | down      |
| 1118   | CHIT1       | down      |
| 1244   | ABCC2       | down      |
| 1299   | COL9A3      | down      |
| 1308   | COL17A1     | down      |
| 1687   | DFNA5       | down      |
| 1847   | DUSP5       | down      |
| 1959   | EGR2        | down      |
| 2213   | FCGR2B      | down      |
| 3310   | HSPA6       | down      |
| 3315   | HSPB1       | down      |
| 3397   | ID1         | down      |
| 3569   | IL6         | down      |
| 3911   | LAMA5       | down      |
| 4283   | CXCL9       | down      |
| 4318   | MMP9        | down      |
| 4547   | MTTP        | down      |
| 5010   | CLDN11      | down      |
| 5054   | SERPINE1    | down      |
| 5360   | PLTP        | down      |
| 5621   | PRNP        | down      |
| 6347   | CCL2        | down      |
| 6352   | CCL5        | down      |
| 6362   | CCL18       | down      |
| 6387   | CXCL12      | down      |
| 6515   | SLC2A3      | down      |
| 6581   | SLC22A3     | down      |
| 7134   | TNNC1       | down      |
| 7305   | TYROBP      | down      |
| 7345   | UCHL1       | down      |
| 8529   | CYP4F2      | down      |
| 9353   | SLIT2       | down      |
| Geneid | Gene Symbol | Direction |
|--------|-------------|-----------|
| 9945   | GFPT2       | down      |
| 10232  | MSLN        | down      |
| 10457  | GPNMB       | down      |
| 10544  | PROCR       | down      |
| 10673  | TNFSF13B    | down      |
| 10974  | C10orf116   | down      |
| 11156  | PTP4A3      | down      |
| 11326  | VSIG4       | down      |
| 23650  | TRIM29      | down      |
| 26049  | FAM169A     | down      |
| 27345  | KCNMB4      | down      |
| 50861  | STMN3       | down      |
| 51330  | TNFRSF12A   | down      |
| 51365  | PLA1A       | down      |
| 51816  | CECR1       | down      |
| 54749  | EPDR1       | down      |
| 57834  | CYP4F11     | down      |
| 60681  | FKBP10      | down      |
| 81035  | COLEC12     | down      |
| 84647  | PLA2G12B    | down      |
| 90293  | KLHL13      | down      |
| 91373  | UAP1L1      | down      |
| 118471 | PRAP1       | down      |
| 140453 | MUC17       | down      |
| 147920 | IGFL2       | down      |
| 151887 | CCDC80      | down      |

Note: *The direction of DEGs computed by the RankProduct method: Each gene was defined as up-regulated (or down-regulated) in non– responders compared with responders if the FDR <0.2 in one dataset and with P-value <0.05 in another.*
**Supplementary Table S4: The 131 CRG 5-FU detected from the CRG 5-FU/L-OHP and GSE52735 dataset**

| Geneid | Gene Symbol | Direction |
|--------|-------------|-----------|
| 9      | NAT1        | up        |
| 136    | ADORA2B     | up        |
| 339    | APOBEC1     | up        |
| 430    | ASCL2       | up        |
| 688    | KLF5        | up        |
| 701    | BUB1B       | up        |
| 891    | CCNB1       | up        |
| 990    | CDC6        | up        |
| 1033   | CDKN3       | up        |
| 1363   | CPE         | up        |
| 1365   | CLDN3       | up        |
| 1366   | CLDN7       | up        |
| 1644   | DDC         | up        |
| 2049   | EPHB3       | up        |
| 2150   | F2RL1       | up        |
| 2487   | FRZB        | up        |
| 2525   | FUT3        | up        |
| 2526   | FUT4        | up        |
| 2762   | GMDS        | up        |
| 2921   | CXCL3       | up        |
| 3171   | FOXA3       | up        |
| 3832   | KIF11       | up        |
| 3960   | LGALS4      | up        |
| 4013   | VWA5A       | up        |
| 4171   | MCM2        | up        |
| 4246   | SCGB2A1     | up        |
| 4306   | NR3C2       | up        |
| 4585   | MUC4        | up        |
| 4751   | NEK2        | up        |
| 4982   | TNFRSF11B   | up        |
| 5122   | PCSK1       | up        |
| 5318   | PKP2        | up        |
| 5357   | PLS1        | up        |
| 5468   | PPARG       | up        |
| 5557   | PRIM1       | up        |
| 5789   | PTPRD       | up        |

(Continued)
| Geneid  | Gene Symbol | Direction |
|---------|-------------|-----------|
| 5918    | RARRES1     | up        |
| 5984    | RFC4        | up        |
| 5985    | RFC5        | up        |
| 6491    | STIL        | up        |
| 6596    | HLTF        | up        |
| 6674    | SPAG1       | up        |
| 6690    | SPINK1      | up        |
| 7033    | TFF3        | up        |
| 7272    | TTK         | up        |
| 7368    | UGT8        | up        |
| 7443    | VRK1        | up        |
| 7504    | XK          | up        |
| 7850    | IL1R2       | up        |
| 8792    | TNFRSF11A   | up        |
| 9055    | PRC1        | up        |
| 9314    | KLF4        | up        |
| 9582    | APOBEC3B    | up        |
| 9787    | DLGAP5      | up        |
| 9928    | KIF14       | up        |
| 9982    | FGFBP1      | up        |
| 10020   | GNE         | up        |
| 10223   | GPA33       | up        |
| 10403   | NDC80       | up        |
| 10418   | SPON1       | up        |
| 10481   | HOXB13      | up        |
| 10551   | AGR2        | up        |
| 10753   | CAPN9       | up        |
| 11004   | KIF2C       | up        |
| 11130   | ZWINT       | up        |
| 23443   | SLC35A3     | up        |
| 26298   | EHF         | up        |
| 26996   | GPR160      | up        |
| 27075   | TSPAN13     | up        |
| 29091   | STXBP6      | up        |
| 29968   | PSAT1       | up        |
| 51514   | DTL         | up        |
| 51809   | GALNT7      | up        |

(Continued)
| Geneid   | Gene Symbol | Direction |
|----------|-------------|-----------|
| 54596    | L1TD1       | up        |
| 54836    | BSPRY       | up        |
| 54845    | ESRP1       | up        |
| 55286    | C4orf19     | up        |
| 55502    | HES6        | up        |
| 55635    | DEPDC1      | up        |
| 55930    | MYO5C       | up        |
| 56992    | KIF15       | up        |
| 57111    | RAB25       | up        |
| 57405    | SPC25       | up        |
| 57475    | PLEKHH1     | up        |
| 57552    | NCEH1       | up        |
| 64073    | C19orf33    | up        |
| 64105    | CENPK       | up        |
| 79170    | PRR15L      | up        |
| 79733    | E2F8        | up        |
| 79782    | LRRRC31     | up        |
| 80150    | ASRGL1      | up        |
| 81575    | APOLD1      | up        |
| 81618    | ITM2C       | up        |
| 84057    | MND1        | up        |
| 84302    | TMEM246     | up        |
| 84419    | C15orf48    | up        |
| 85315    | PAQR8       | up        |
| 124975   | GGT6        | up        |
| 138065   | RNF183      | up        |
| 139886   | SPIN4       | up        |
| 148170   | CDC42EP5    | up        |
| 148418   | SAMD13      | up        |
| 149175   | MANEAL      | up        |
| 150209   | AIFM3       | up        |
| 151827   | LRRC34      | up        |
| 152100   | CMC1        | up        |
| 192134   | B3GNT6      | up        |
| 222171   | PRR15       | up        |
| 253012   | HEPACAM2    | up        |
| 255738   | PCSK9       | up        |

(Continued)
| Geneid  | Gene Symbol | Direction* |
|---------|-------------|------------|
| 282809  | POC1B       | up         |
| 285704  | RGMB        | up         |
| 340277  | FAM221A     | up         |
| 401546  | C9orf152    | up         |
| 100133941 | CD24      | up         |
| 341     | APOC1       | down       |
| 978     | CDA         | down       |
| 1118    | CHIT1       | down       |
| 1959    | EGR2        | down       |
| 3310    | HSPA6       | down       |
| 3315    | HSPB1       | down       |
| 4547    | MTTP        | down       |
| 5010    | CLDN11      | down       |
| 6347    | CCL2        | down       |
| 7134    | TNNC1       | down       |
| 8529    | CYP4F2      | down       |
| 9353    | SLIT2       | down       |
| 10457   | GPNMB       | down       |
| 10974   | C10orf116   | down       |
| 84647   | PLA2G12B    | down       |
| 151887  | CCDC80      | down       |

Note: *The direction of DEGs computed by the RankProduct method: Each gene was defined as up-regulated (or down-regulated) in non-responders compared with responders in both CRG5-FU/L-OHP and the GSE52735 dataset (FDR<0.2).
**Supplementary Table S5: The consistency scores of the top-ranked 300(1500) BD genes or ID genes of 5-FU and L-OHP**

| Dataset   | Cell line      | Gene set | Method | Overlapped DEGᵃ | Consistent DEG(%)ᵇ | Binominal P-value |
|-----------|----------------|----------|--------|-----------------|--------------------|-------------------|
| E-MEXP-390| HCT116 (colon)| BD       | FC     | 1312(575)       | 97.13(97.22)       | <5.55E-16(<5.55E-16) |
|           |                |          | AD     | 1980(888)       | 80.51(81.10)       | <5.55E-16(<5.55E-16) |
|           |                | ID₁₀     | FC     | 681(281)        | 61.38(65.12)       | 1.55E-09(2.23E-07)  |
|           |                |          | AD     | 1783(832)       | 48.63(44.11)       | >1.00E-01(>1.00E-0.1) |
|           |                | ID₁₂     | FC     | 784(282)        | 79.72(82.27)       | <5.55E-16(<5.55E-16) |
|           |                |          | AD     | 1834(807)       | 70.61(73.73)       | <5.55E-16(<5.55E-16) |
|           |                | ID₂₄     | FC     | 580(196)        | 66.55(70.92)       | 5.55E-16(2.17E-09)  |
|           |                |          | AD     | 1921(917)       | 91.10(94.44)       | <5.55E-16(<5.55E-16) |

ᵃThe number of BD genes (ID genes) of 5-FU overlapped with BD genes (ID genes) of L-OHP;
ᵇThe consistency score of BD genes (ID genes) of 5-FU and BD genes (ID genes) of L-OHP;
Supplementary Table S6: The consistency scores of CRG S-FU and the top-ranked 300(1500) BD or ID genes

| Dataset     | Cell line | Gene set | Method | Overlapped DEG* | Consistent DEG(%) | Binominal P-value |
|-------------|-----------|----------|--------|----------------|-------------------|-------------------|
| E-MEXP-390  | HCT116    | BD       | FC     | 26(18)         | 50.00 (55.56)     | >1.00E-01 (>1.00E-01) |
|             |           | AD       |        | 38(22)         | 65.79 (68.18)     | 3.53E-02 (6.69E-02) |
| ID6         |           | FC       |        | 32(17)         | 46.88 (52.94)     | >1.00E-01 (>1.00E-01) |
|             |           | AD       |        | 37(21)         | 40.54 (38.10)     | >1.00E-01 (>1.00E-01) |
| ID12        |           | FC       |        | 38(23)         | 86.84 (91.30)     | 2.13E-06 (3.30E-05) |
|             |           | AD       |        | 52(31)         | 80.77 (87.10)     | 4.53E-06 (1.70E-05) |
| ID24        |           | FC       |        | 30(16)         | 66.67 (62.60)     | 4.94E-02 (>1.00E-01) |
|             |           | AD       |        | 41(25)         | 75.61 (72.00)     | 7.25E-04 (2.16E-02) |
Supplementary Table S7: The consistency scores of CRG\textsubscript{5-FU/L-OHP} and the top-ranked 1500 BD or ID genes

| Data source | Drug    | Cell line | Gene set | Method | Overlapped DEG\textsuperscript{b} | Consistent DEG(%) | Binominal P-value |
|-------------|---------|-----------|----------|--------|-------------------------------|-------------------|------------------|
| E-MEXP-390  | 5-FU/L-OHP | HCT116    | BD\textsubscript{two} | FC     | 24                            | 45.83             | >1.00E-0.1       |
|             |         |           |          | AD     | 25                            | 60.00             | >1.00E-0.1       |
|             |         |           | ID\textsubscript{two-6} | FC     | 5                             | 40.00             | >1.00E-0.1       |
|             |         |           |          | AD     | 12                            | 75.00             | 7.30E-02         |
|             |         |           | ID\textsubscript{two-12} | FC     | 6                             | 50.00             | >1.00E-0.1       |
|             |         |           |          | AD     | 18                            | 50.00             | >1.00E-0.1       |
|             |         |           | ID\textsubscript{two-24} | FC     | 3                             | 100.00            | >1.00E-0.1       |
|             |         |           |          | AD     | 23                            | 82.61             | 1.30E-03         |

| E-MEXP-390  | 5-FU | HCT116    | BD | FC | 45 | 53.33 | >1.00E-0.1 |
|             |      |           | AD | 44 | 68.18 | 1.13E-02  |
|             |      |           | ID\textsubscript{6} | FC | 46 | 54.35 | >1.00E-0.1 |
|             |      |           |          | AD | 40 | 50.00 | >1.00E-0.1 |
|             |      |           | ID\textsubscript{12} | FC | 46 | 82.61 | 4.62E-06  |
|             |      |           |          | AD | 51 | 78.43 | 2.85E-05  |
|             |      |           | ID\textsubscript{24} | FC | 47 | 53.19 | >1.00E-0.1 |
|             |      |           |          | AD | 46 | 73.91 | 8.21E-04  |

| E-MEXP-390  | L-OHP | HCT116    | BD | FC | 59 | 47.46 | >1.00E-0.1 |
|             |       |           | AD | 43 | 55.81 | >1.00E-0.1 |
|             |       |           | ID\textsubscript{6} | FC | 42 | 47.62 | >1.00E-0.1 |
|             |       |           |          | AD | 38 | 57.89 | >1.00E-0.1 |
|             |       |           | ID\textsubscript{12} | FC | 58 | 17.24 | >1.00E-0.1 |
|             |       |           |          | AD | 58 | 25.86 | >1.00E-0.1 |
|             |       |           | ID\textsubscript{24} | FC | 42 | 80.95 | 3.44E-05  |
|             |       |           |          | AD | 42 | 88.10 | 2.22E-07  |

| GSE10405    | L-OHP | DLD1      | BD | FC | 8  | 87.50 | 3.52E-02  |
|             |       | HT29      |     | AD | 8  | 87.50 | 3.52E-02  |
|             |       | LS513     |     | FC | 8  | 37.50 | >1.00E-0.1|
|             |       | Lovo      |     | AD | 8  | 50.00 | >1.00E-0.1|

\textsuperscript{a}The number of candidate drug resistance genes overlapped with CRG\textsubscript{5-FU/L-OHP};
\textsuperscript{b}The consistency score of candidate drug resistance genes and CRG\textsubscript{5-FU/L-OHP}. 
Supplementary Table S8: The average expression levels of DEGs exclusively detected by FC or AD and the corresponding consistency scores with CRG_{5-FU-L-OHP} or ID_{clinical} genes

| Gene set  | Cell line sample | Method | Average expression | Overlapped DEG | Consistent DEG(%) | Binominal P-value |
|-----------|------------------|--------|--------------------|----------------|-------------------|------------------|
| ID_{two-24} | parental cell line treated with 5-FU for 24h | FC | 212.93 | 7 | 57.14 | >1.00E-0.1 |
| | resistant cell line treated with 5-FU for 24h | | 238.03 | 7 | 57.14 | >1.00E-0.1 |
| | parental cell line treated with 5-FU for 24h | AD | 1992.72 | 35 | 82.86 | 5.84E-05 |
| | resistant cell line treated with 5-FU for 24h | | 2322.72 | 35 | 82.86 | 5.84E-05 |
| | parental cell line treated with L-OHP for 24h | FC | 189.94 | 7 | 57.14 | >1.00E-0.1 |
| | resistant cell line treated with L-OHP for 24h | | 215.84 | 7 | 57.14 | >1.00E-0.1 |
| | parental cell line treated with L-OHP for 24h | AD | 1898.34 | 35 | 82.86 | 5.84E-05 |
| | resistant cell line treated with L-OHP for 24h | | 2315.57 | 35 | 82.86 | 5.84E-05 |
| BD | parental cell line | FC | 124.36 | 40 | 35.00 | >1.00E-0.1 |
| | 5-FU resistant cell line | | 109.79 | 40 | 35.00 | >1.00E-0.1 |
| | parental cell line | AD | 2187.87 | 36 | 66.67 | 3.26E-02 |
| | 5-FU resistant cell line | | 2178.89 | 36 | 66.67 | 3.26E-02 |
| ID_{24} | parental cell line treated with 5-FU for 24h | FC | 132.29 | 52 | 44.23 | >1.00E-0.1 |
| | resistant cell line treated with 5-FU for 24h | | 133.43 | 52 | 44.23 | >1.00E-0.1 |
| | parental cell line treated with 5-FU for 24h | AD | 1859.91 | 52 | 69.23 | 3.89E-03 |
| | resistant cell line treated with 5-FU for 24h | | 1979.44 | 52 | 69.23 | 3.89E-03 |
| ID_{two-24} | parental cell line treated with 5-FU for 24h | FC | 129.16 | 54 | 57.41 | >1.00E-0.1 |
| | resistant cell line treated with 5-FU for 24h | | 119.5 | 54 | 57.41 | >1.00E-0.1 |
| | parental cell line treated with 5-FU for 24h | AD | 2205.26 | 131 | 73.28 | 4.70E-08 |
| | resistant cell line treated with 5-FU for 24h | | 2537.18 | 131 | 73.28 | 4.70E-08 |
| | parental cell line treated with L-OHP for 24h | FC | 126.76 | 54 | 57.41 | >1.00E-0.1 |
| | resistant cell line treated with L-OHP for 24h | | 118.39 | 54 | 57.41 | >1.00E-0.1 |
| | parental cell line treated with L-OHP for 24h | AD | 2114.29 | 131 | 73.28 | 4.70E-08 |
| | resistant cell line treated with L-OHP for 24h | | 2457.48 | 131 | 73.28 | 4.70E-08 |

Abbreviations:
aID_{two-24} genes compared with CRG_{5-FU-L-OHP};
bID_{two-24} genes compared with ID_{clinical} genes.
## Supplementary Table S9: 70 genes of 5-FU resistance and 65 genes of L-OHP resistance

| Drug  | Gene Symbol | FC value | AD value | Direction |
|-------|-------------|----------|----------|-----------|
| 5-FU  | BUB1B       | 1.02     | 439.79   | up        |
|       | B4GALT4     | 1.04     | 76.99    | up        |
|       | CCDC58      | 1.02     | 177.84   | up        |
|       | CCNB1       | 1.05     | 443.07   | up        |
|       | CD24        | 1.03     | 155.64   | up        |
|       | CENPK       | 1.03     | 76.99    | up        |
|       | CLDN3       | 1.04     | 77.80    | up        |
|       | CMC1        | 1.04     | 272.91   | up        |
|       | DEPDC1      | 1.02     | 92.57    | up        |
|       | DLGAP5      | 1.02     | 369.33   | up        |
|       | EBAG9       | 1.03     | 190.08   | up        |
|       | ESRP1       | 1.02     | 280.04   | up        |
|       | FAM171A1    | 1.03     | 281.89   | up        |
|       | GNE         | 1.04     | 54.55    | up        |
|       | GOLPH3L     | 1.02     | 170.37   | up        |
|       | GPR160      | 1.04     | 128.67   | up        |
|       | HES6        | 1.02     | 199.86   | up        |
|       | HLTF        | 1.01     | 271.28   | up        |
|       | HOXA13      | 1.03     | 25.51    | up        |
|       | IMPA2       | 1.09     | 576.44   | up        |
|       | KIAA1211    | 1.06     | 69.34    | up        |
|       | KIF14       | 1.05     | 360.68   | up        |
|       | KIF20A      | 1.02     | 168.29   | up        |
|       | MANEAL      | 1.02     | 79.43    | up        |
|       | MAOA        | 1.04     | 85.02    | up        |
|       | MCM2        | 1.01     | 213.23   | up        |
|       | MND1        | 1.03     | 116.63   | up        |
|       | MYO5C       | 1.02     | 221.51   | up        |
|       | NDC80       | 1.06     | 519.47   | up        |
|       | NR3C2       | 1.04     | 15.83    | up        |
|       | NR5A2       | 1.06     | 12.53    | up        |
|       | PAIP1       | 1.04     | 336.38   | up        |
|       | PLAGL1      | 1.04     | 111.00   | up        |
|       | PLEKHH1     | 1.08     | 138.95   | up        |
|       | PLS1        | 1.01     | 152.86   | up        |
|       | PPARG       | 1.05     | 143.69   | up        |

(Continued)
| Drug | Gene Symbol | FC value | AD value | Direction |
|------|-------------|----------|----------|-----------|
| 5-FU | PRC1        | 1.02     | 563.74   | up        |
|      | PSAT1       | 1.01     | 244.31   | up        |
|      | RAB25       | 1.01     | 101.14   | up        |
|      | RFC4        | 1.01     | 267.77   | up        |
|      | RNASE4      | 1.08     | 89.26    | up        |
|      | SGOL2       | 1.03     | 121.68   | up        |
|      | SLC16A14    | 1.04     | 51.90    | up        |
|      | SLC35A1     | 1.03     | 234.17   | up        |
|      | SLC35A3     | 1.04     | 68.34    | up        |
|      | SPTSSA      | 1.02     | 101.42   | up        |
|      | SRI         | 1.06     | 180.90   | up        |
|      | STXB6       | 1.08     | 14.70    | up        |
|      | SUDS3       | 1.05     | 203.54   | up        |
|      | SYTL2       | 1.03     | 100.64   | up        |
|      | TDP2        | 1.02     | 210.86   | up        |
|      | TSPAN13     | 1.02     | 365.85   | up        |
|      | TST         | 1.01     | 108.90   | up        |
|      | TTK         | 1.02     | 241.92   | up        |
|      | TYMS        | 1.04     | 648.87   | up        |
|      | UNG         | 1.03     | 415.74   | up        |
|      | VWA5A       | 1.04     | 83.72    | up        |
|      | XK          | 1.05     | 58.94    | up        |
|      | ZNF468      | 1.06     | 133.06   | up        |
|      | ZWINT       | 1.02     | 903.01   | up        |
|      | ABC2C       | 1.03     | 96.44    | down      |
|      | DUSP5       | 1.01     | 231.34   | down      |
|      | LAMA5       | 1.02     | 171.80   | down      |
|      | SERPINE1    | 1.05     | 57.56    | down      |
|      | PLTP        | 1.04     | 27.92    | down      |
|      | TNNC1       | 1.11     | 50.50    | down      |
|      | UCHL1       | 1.05     | 25.91    | down      |
|      | CYP4F2      | 1.04     | 28.27    | down      |
|      | PROCR       | 1.02     | 195.37   | down      |
|      | VSIG4       | 1.06     | 40.57    | down      |
| L-OHP | ALYREF      | 1.05     | 1351.19  | up        |
|      | ANG         | 1.04     | 32.78    | up        |
|      | BUB1B       | 1.04     | 646.75   | up        |

(Continued)
| Drug   | Gene Symbol | FC value | AD value | Direction |
|--------|-------------|----------|----------|-----------|
| L-OHP  | CCDC58      | 1.02     | 256.12   | up        |
|        | CCNB1       | 1.02     | 221.64   | up        |
|        | CCNE2       | 1.13     | 270.36   | up        |
|        | CD24        | 1.02     | 135.36   | up        |
|        | CDC6        | 1.07     | 427.31   | up        |
|        | CDKN3       | 1.04     | 550.51   | up        |
|        | CENPK       | 1.07     | 103.74   | up        |
|        | CENPU       | 1.06     | 139.69   | up        |
|        | CHGA        | 1.03     | 13.48    | up        |
|        | CLDN3       | 1.04     | 60.97    | up        |
|        | CLDN7       | 1.03     | 499.85   | up        |
|        | CMC1        | 1.04     | 305.48   | up        |
|        | DLGAP5      | 1.02     | 205.55   | up        |
|        | DTL         | 1.07     | 418.38   | up        |
|        | E2F8        | 1.06     | 165.21   | up        |
|        | EBAG9       | 1.02     | 166.11   | up        |
|        | ESRP1       | 1.02     | 322.77   | up        |
|        | F2RL1       | 1.02     | 321.75   | up        |
|        | FAIM        | 1.04     | 71.36    | up        |
|        | HES6        | 1.02     | 177.93   | up        |
|        | HLTF        | 1.02     | 358.03   | up        |
|        | HPDL        | 1.05     | 20.85    | up        |
|        | IMPA2       | 1.08     | 327.21   | up        |
|        | ITM2C       | 1.04     | 493.52   | up        |
|        | KIF11       | 1.05     | 211.65   | up        |
|        | KIF14       | 1.03     | 128.62   | up        |
|        | KIF20A      | 1.02     | 140.89   | up        |
|        | KIF2C       | 1.03     | 350.41   | up        |
|        | LGALS2      | 1.04     | 9.27     | up        |
|        | MANEAL      | 1.05     | 130.07   | up        |
|        | MCM2        | 1.05     | 1276.48  | up        |
|        | MND1        | 1.08     | 252.19   | up        |
|        | MYO5C       | 1.02     | 187.17   | up        |
|        | NDC80       | 1.04     | 246.25   | up        |
|        | NEK2        | 1.03     | 139.92   | up        |
|        | NUSAP1      | 1.04     | 564.83   | up        |
|        | ORC1        | 1.06     | 103.89   | up        |

(Continued)
| Drug | Gene Symbol | FC value | AD value | Direction$^a$ |
|------|-------------|----------|----------|--------------|
| L-OHP | PAIP1       | 1.03     | 254.04   | up           |
|      | PCSK9       | 1.04     | 128.89   | up           |
|      | PDZK11P1    | 1.03     | 12.34    | up           |
|      | PLS1        | 1.01     | 115.53   | up           |
|      | PRC1        | 1.04     | 1029.61  | up           |
|      | PRIM1       | 1.05     | 926.98   | up           |
|      | PSAT1       | 1.03     | 511.77   | up           |
|      | RAB25       | 1.03     | 506.02   | up           |
|      | RFC4        | 1.05     | 855.13   | up           |
|      | RFC5        | 1.05     | 360.68   | up           |
|      | SLC9A2      | 1.04     | 10.65    | up           |
|      | SPAG5       | 1.03     | 139.38   | up           |
|      | SPC25       | 1.08     | 255.39   | up           |
|      | SPIN4       | 1.05     | 260.68   | up           |
|      | STIL        | 1.03     | 159.80   | up           |
|      | STXBP6      | 1.05     | 9.52     | up           |
|      | TTK         | 1.03     | 296.06   | up           |
|      | TYMS        | 1.03     | 278.62   | up           |
|      | UNG         | 1.06     | 805.10   | up           |
|      | USP1        | 1.05     | 316.55   | up           |
|      | VRK1        | 1.03     | 245.80   | up           |
|      | VSIG2       | 1.04     | 25.49    | up           |
|      | ZG16        | 1.05     | 26.82    | up           |
|      | ZWINT       | 1.04     | 1235.85  | up           |
|      | IGFL2       | 1.06     | 111.20   | down         |

$^a$The direction of DEGs: Each gene was defined as up-regulated (or downregulated) in resistant cells compared with parental cells if the value of FC or AD was larger (or smaller) than zero.
Supplementary Table S10: Summaries of the top 20 ID24 genes ranked by AD method for 5-FU and L-OHP, respectively. All of the genes were up-regulated in the resistant cells compared with the sensitive cells.

| Drug | Gene Symbol | Summary |
|------|-------------|---------|
| 5-FU | ZWINT | ZW10 interacting kinetochore protein; The encoded protein is involved in kinetochore function and overexpression of ZWINT stimulates cell growth [1]. |
|      | TYMS | thymidylate synthetase; It is a target for 5-FU. High expression of this gene activates 5-FU resistance [2]. |
|      | IMPA2 | inositol(myo)-1(or 4)-monophosphatase 2; The encoded protein catalyzes the dephosphorylation of inositol monophosphate. |
|      | PRC1 | protein regulator of cytokinesis 1; This gene encodes a protein that is involved in cytokinesis and acts as both tumor suppressors and oncogenes [3]. |
|      | NDC80 | NDC80 kinetochore complex component; This protein is required for proper chromosome segregation, which might be one of the mechanisms of 5-FU action [4, 5]. |
|      | CCNB1 | cyclin B1; The protein encoded by this gene is a regulatory protein involved in mitosis, which could be an anti-cancer drug target [6]. |
|      | BUB1B | BUB1 mitotic checkpoint serine/threonine kinase B; |
|      | UNG | uracil-DNA glycosylase; UNG initiated base excision repair, which could stimulate the development of be related to L-OHP resistance [7]. |
|      | DLGAP5 | discs, large (Drosophila) homolog-associated protein 5; Up-regulation of DLGAP5 contributes to hepatocellular carcinoma cells tumorigenesis by promoting cell proliferation [8]. |
|      | TSPAN13 | tetraspanin 13; The proteins mediate signal transduction events that play a role in the regulation of cell development, activation, growth and motility. |
|      | KIF14 | kinesin family member 14; KIF14 knockdown clearly enhanced chemosensitivity to docetaxel in breast cancer and this gene played a role in response to cytotoxic chemotherapy [9]. |
|      | PAIP1 | poly(A) binding protein interacting protein 1; |
|      | FAM171A1 | family with sequence similarity 171, member A1; |
|      | ESRP1 | epithelial splicing regulatory protein 1; ESRP1 is re-expressed in the lymph nodes, where carcinoma cells metastasize and colonize [10]. |
|      | CMC1 | C-x(9)-C motif containing 1; |
|      | HLTF | helicase-like transcription factor; The encoded protein plays a pivotal role in the template-switching pathway of DNA damage tolerance [11, 12]. |
|      | RFC4 | replication factor C (activator 1) 4, 37kDa; This inhibition of RFC4 expression correlated with a decrease in cellular proliferation, increased levels of apoptosis and a sensitizing of the cells to the DNA-damaging chemotherapeutic agents [13]. |
|      | PSAT1 | phosphoserine aminotransferase 1; |
|      | TTK | TTK protein kinase; The encoded protein is associated with cell proliferation and essential for chromosome alignment at the centromere during mitosis [14, 15]. |
|      | SLC35A1 | solute carrier family 35 (CMP-sialic acid transporter), member A1; SLC35A1 is a member of solute carriers (SLCs) and its overexpression can activate the process of absorption and transport of cell inhibitors [16]. |

(Continued)
| Drug   | Gene Symbol | Summary                                                                                                                                 |
|--------|-------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| L-OHP  | ALYREF      | Aly/REF export factor;                                                                                                                  |
|        | MCM2        | minichromosome maintenance complex component 2; The protein encoded by this gene is involved in replication and promotes tumor cell proliferation [14]. |
|        | ZWINT       | ZW10 interacting kinetochore protein; The encoded protein is involved in kinetochore function and overexpression of ZWINT stimulates cell growth [1]. |
|        | PRC1        | protein regulator of cytokinesis 1; This gene encodes a protein that is involved in cytokinesis.                                        |
|        | PRIM1       | primase, DNA, polypeptide 1 (49kDa);                                                                                                    |
|        | RFC4        | replication factor C (activator 1) 4, 37kDa; This inhibition of RFC4 expression correlated with a decrease in cellular proliferation, increased levels of apoptosis and a sensitizing of the cells to the DNA-damaging chemotherapeutic agents [13]. |
|        | UNG         | uracil-DNA glycosylase; UNG initiated base excision repair, which could stimulate the development of being related to L-OHP resistance [7]. |
|        | BUB1B       | BUB1 mitotic checkpoint serine/threonine kinase B;                                                                                       |
|        | NUSAP1      | nucleolar and spindle associated protein 1; NUSAP1 influences the DNA damage response by controlling BRCA1 protein levels [17].            |
|        | CDKN3       | cyclin-dependent kinase inhibitor 3; The gene plays a key role in regulating cell division and tumorigenesis [18].                     |
|        | PSAT1       | phosphoserine aminotransferase 1; Overexpression of PSAT1 stimulates cell growth and increases chemoresistance of colon cancer cells to L-OHP [19]. |
|        | RAB25       | member RAS oncogene family; RAB25 is a tumour suppressor in colon carcinogenesis and shows an effect comparable with blocking the PI3K/AKT pathway and contributes to cisplatin resistance in human epithelial ovarian [20, 21]. |
|        | CLDN7       | claudin 7; Defective Claudin-7 increases the tumorigenicity of colorectal cancer cells [22].                                            |
|        | ITM2C       | integral membrane protein 2C;                                                                                                            |
|        | CDC6        | cell division cycle 6; The encoded protein plays a critical role in carcinogenesis [23].                                                 |
|        | DTL         | denticleless E3 ubiquitin protein ligase homolog (Drosophila);                                                                         |
|        | RFC5        | replication factor C (activator 1) 5, 36.5kDa; The encoded protein is related to mismatch repair [24].                                    |
|        | HLTF        | helicase-like transcription factor; The encoded protein plays a pivotal role in the template-switching pathway of DNA damage tolerance [11, 12]. |
|        | KIF2C       | kinesin family member 2C;                                                                                                               |
|        | IMPA2       | inositol(myo)-1(or 4)-monophosphatase 2; The encoded protein catalyzes the dephosphorylation of inositol monophosphate.                |
Supplementary Table S11: The enriched pathways of the top-ranked 3000 DEGs. \( p(<0.05) \) was adjusted by Benjamini and Hochberg (FDR<0.1)

| Drug | Method | KEGG Pathway | \( p \)-value | Reference |
|------|--------|---------------|---------------|-----------|
| 5-FU | FC     | Steroid biosynthesis | 2.40E-06 |            |
|      |        | Arachidonic acid metabolism | 1.69E-03 |            |
|      |        | Cytokine-cytokine receptor interaction | 2.44E-07 |            |
|      |        | Neuroactive ligand-receptor interaction | 9.00E-06 |            |
|      |        | **p53 signaling pathway** | **8.59E-12** | [25] |
|      |        | Complement and coagulation cascades | 8.61E-05 |            |
|      | AD     | Glycolysis / Gluconeogenesis | 1.02E-04 | [26] |
|      |        | **Steroid biosynthesis** | **3.57E-03** |            |
|      |        | Oxidative phosphorylation | 3.69E-07 |            |
|      |        | Glutathione metabolism | 2.81E-03 | [27, 28] |
|      |        | N-Glycan biosynthesis | 3.62E-03 |            |
|      |        | Amino sugar and nucleotide sugar metabolism | 7.28E-03 |            |
|      |        | Pyruvate metabolism | 1.94E-04 | [26, 29] |
|      |        | Propanoate metabolism | 3.70E-03 |            |
|      |        | Carbon metabolism | 5.48E-03 | [26] |
|      |        | Ribosome biogenesis in eukaryotes | 5.44E-07 |            |
|      |        | Ribosome | 0.00E+00 |            |
|      |        | RNA transport | 9.21E-06 |            |
|      |        | mRNA surveillance pathway | 6.79E-05 |            |
|      |        | Basal transcription factors | 6.53E-04 |            |
|      |        | Spliceosome | 1.92E-11 | [30] |
|      |        | Proteasome | 2.03E-07 | [31] |
|      |        | Protein export | 4.52E-05 |            |
|      |        | Cell cycle | 4.12E-05 | [32] |
|      |        | Protein processing in endoplasmic reticulum | 2.04E-08 | [33, 34] |
|      |        | **p53 signaling pathway** | **<1.11E-16** | [25, 35] |
|      |        | Collecting duct acid secretion | 6.39E-04 |            |
| L-OHP| FC     | Steroid biosynthesis | 1.36E-04 |            |
|      |        | **Pyrimidine metabolism** | **1.81E-05** | [36] |
|      |        | Biosynthesis of unsaturated fatty acids | 9.42E-04 |            |
|      |        | Fatty acid metabolism | 2.66E-03 | [26] |
|      |        | **DNA replication** | **9.10E-15** | [32] |
|      |        | Base excision repair | 1.68E-05 | [7] |
|      |        | Nucleotide excision repair | 1.23E-03 | [7] |
|      |        | Mismatch repair | 8.39E-06 | [7, 37] |
|      |        | Homologous recombination | 1.03E-04 |            |

(Continued)
| Drug   | Method | KEGG Pathway                              | P-value     | Reference |
|--------|--------|-------------------------------------------|-------------|-----------|
| L-OHP  | FC     | Fanconi anemia pathway                    | 2.19E-05    |           |
|        |        | Cell cycle                                | 8.48E-11    | [32]      |
|        |        | Cytokine-cytokine receptor interaction    | 2.49E-06    |           |
|        |        | Neuroactive ligand-receptor interaction   | 8.96E-08    |           |
|        |        | Olfactory transduction                    | 7.77E-05    |           |
|        | AD     | Glycolysis / Gluconeogenesis              | 8.07E-06    | [26]      |
|        |        | Citrate cycle (TCA cycle)                 | 2.85E-05    | [26]      |
|        |        | Pentose phosphate pathway                 | 5.09E-04    |           |
|        |        | Fatty acid degradation                    | 1.38E-02    |           |
|        |        | Oxidative phosphorylation                 | 1.48E-14    |           |
|        |        | **Pyrimidine metabolism**                 | 9.42E-05    | [36]      |
|        |        | Cysteine and methionine metabolism        | 2.49E-03    |           |
|        |        | Arginine and proline metabolism           | 3.24E-03    |           |
|        |        | Glutathione metabolism                    | 9.56E-04    | [27, 28]  |
|        |        | Pyruvate metabolism                       | 2.46E-06    | [26, 29]  |
|        |        | Propanoate metabolism                     | 5.43E-04    |           |
|        |        | Aminoacyl-tRNA biosynthesis                | 7.41E-03    |           |
|        |        | Carbon metabolism                         | 1.40E-09    | [26]      |
|        |        | 2-Oxocarboxylic acid metabolism           | 4.41E-03    |           |
|        |        | Biosynthesis of amino acids               | 6.95E-07    |           |
|        |        | Ribosome biogenesis in eukaryotes         | 2.15E-05    |           |
|        |        | Ribosome                                  | <1.11E-16   |           |
|        |        | RNA transport                             | 6.33E-11    |           |
|        |        | mRNA surveillance pathway                 | 2.96E-03    |           |
|        |        | **DNA replication**                       | 1.02E-10    | [32, 37]  |
|        |        | Spliceosome                                | 9.77E-15    | [30]      |
|        |        | Proteasome                                 | 1.49E-11    | [31]      |
|        |        | Protein export                            | 5.00E-05    |           |
|        |        | **Base excision repair**                  | 1.29E-06    | [7]       |
|        |        | **Nucleotide excision repair**            | 4.21E-06    | [7]       |
|        |        | **Mismatch repair**                       | 2.44E-05    | [7, 37]   |
|        |        | **Cell cycle**                            | 3.81E-12    | [32]      |
|        |        | Oocyte meiosis                            | 6.53E-03    |           |
|        |        | Protein processing in endoplasmic reticulum | 1.61E-05 | [33, 34] |
|        |        | Phagosome                                 | 1.15E-02    |           |
|        |        | p53 signaling pathway                     | 6.75E-06    | [25, 35]  |

Note: Bold parts are common pathways that DEGs ranked by FC or AD significantly enriched in.
Supplementary Table S12: Several inhibitors which have been reported to target the corresponding pathways

| KEGG Pathway                  | Inhibitor                                                                 |
|-------------------------------|---------------------------------------------------------------------------|
| Pyrimidine metabolism         | GW776; 5-chloro-2,4-dihydroxypyridine (CDHP; gimestat); potassium oxonate (OXO; otastat) [38] |
| Pyruvate metabolism           | Dichloroacetate (DCA) [39]                                               |
| Glycolysis / Gluconeogenesis  | 2-deoxy-d-glucose [40–42]                                                 |
| Cell cycle                    | AZD7762; Roscovitine; CGP-60474; CGP-082996; 681640; PD-0332991 [43]      |
| DNA replication               | AZD7762; MK-8776 (SCH900776); IC-83 (LY2603618) [32]; Camptothecin [43]   |
| DNA Repair                    | AZD-2281; ABT-888; KU-55933; NU-7441 [43]                                |
| p53 signaling pathway         | Cyclic Pifithrin-α hydrobromide (ab144327); cyclic dehydrated 6b analogue [44, 45] |
| Proteasome                    | bortezomib [46]                                                           |
## Supplementary Table S13: The consistency scores of ID\textsubscript{clinical} genes and CRG\textsubscript{5-FU/L-OHP} (CRG\textsubscript{5-FU}) or the top-ranked 3000 (top-ranked 1500) ID genes

| Drug       | Gene set | Method | Overlapped DEG\textsuperscript{a} | Consistent DEG(%) | Binominal P-value |
|------------|----------|--------|-----------------------------------|------------------|-------------------|
| 5-FU/L-OHP | CRG\textsubscript{5-FU/L-OHP} | RankProduct | 161 | 83.85 | <1.11E-16 |
| 5-FU       | CRG\textsubscript{5-FU}     | RankProduct | 78 | 88.46 | <1.11E-16 |
| 5-FU/L-OHP | ID\textsubscript{two-6}     | FC      | 49 (27) | 36.73 (33.33) | >1.00E-0.1 (>1.00E-0.1) |
|            |          | AD      | 95 (43) | 56.84 (65.12) | >1.00E-0.1 (3.30E-02) |
| 5-FU/L-OHP | ID\textsubscript{two-12}    | FC      | 87 (40) | 47.13 (37.50) | >1.00E-0.1 (1.00E-0.1) |
|            |          | AD      | 138 (63) | 44.20 (39.68) | >1.00E-0.1 (1.00E-0.1) |
| 5-FU/L-OHP | ID\textsubscript{two-24}    | FC      | 63 (27) | 60.32 (51.58) | 6.50E-02 (1.00E-0.1) |
|            |          | AD      | 140 (59) | 73.57 (77.97) | 1.09E-08 (9.58E-06) |
| 5-FU       | ID\textsubscript{6}         | FC      | 372 (214) | 54.84 (55.14) | 3.47E-02 (7.55E-02) |
|            |          | AD      | 338 (164) | 57.69 (59.15) | 2.73E-03 (1.16E-02) |
| 5-FU       | ID\textsubscript{12}        | FC      | 412 (250) | 58.50 (58.40) | 3.29E-04 (4.69E-03) |
|            |          | AD      | 372 (199) | 57.53 (58.79) | 2.14E-03 (7.87E-03) |
| 5-FU       | ID\textsubscript{24}        | FC      | 395 (234) | 64.30 (61.97) | 7.02E-09 (1.52E-04) |
|            |          | AD      | 322 (159) | 67.08 (67.30) | 4.31E-10 (7.69E-06) |
| L-OHP      | ID\textsubscript{6}         | FC      | 300 (174) | 40.33 (37.36) | >1.00E-0.1 (>1.00E-0.1) |
|            |          | AD      | 301 (140) | 49.83 (51.43) | >1.00E-0.1 (>1.00E-0.1) |
| L-OHP      | ID\textsubscript{12}        | FC      | 386 (227) | 31.35 (21.59) | >1.00E-0.1 (>1.00E-0.1) |
|            |          | AD      | 339 (209) | 34.22 (28.23) | >1.00E-0.1 (>1.00E-0.1) |
| L-OHP      | ID\textsubscript{24}        | FC      | 312 (172) | 62.50 (65.70) | 5.91E-06 (2.33E-05) |
|            |          | AD      | 282 (141) | 68.44 (75.18) | 2.76E-10 (8.47E-10) |