# WEE1 inhibition delays resistance to CDK4/6 inhibitor and antiestrogen treatment in estrogen receptor-positive MCF7 breast cancer cells: experiments and mathematical modeling

Wei He, Diane M. Demas, Pavel Kraikivski, Ayesha N. Shajahan-Haq and William T. Baumann

## Supplementary Note 1

The literature references for the numbered interactions of the signaling pathway and drugs, shown in Fig. 4A, are as follows:

1. E2 binds to ER[1]; 2. ICI binds to ER[2]; 3. E2:ER increases transcription of c-Myc[3]; 4. E2:ER increases transcription of cyclinE1[4]; 5. E2:ER increases transcription of cyclinD1[3]; 6. c-Myc inhibits transcription of p21[5]; 7. CyclinD1 binds to Cdk4[6]; 8. CylinD1 binds to Cdk6[6]; 9. p21 binds to cyclinD1:Cdk4[7]; 10. p21 binds to cyclinD1:Cdk6[7]; 11. CyclinE1 binds to Cdk2[3]; 12. p21 binds to cyclinE1:Cdk2[8]; 13. Palbociclib binds to Cdk4[9]; 14. Palbociclib binds Cdk6[9]; 15. Palbociclib binds to cyclinD1:Cdk4[9]; 16. Palbociclib binds to cyclinD1:Cdk6[9]; 17. Palbociclib binds to cyclinD1:Cdk4:p21[10]; 18. Palbociclib binds to cyclinD1:Cdk6:p21[10]; 19. CyclinD1:Cdk4/6 phosphorylates RB1 to RB1-p[3]; 20. CyclinE1:Cdk2 phosphorylates RB1-p to RB1-pp[3]; 21. RB1 binds to E2F[11]; 22. RB1-p binds to E2F[11]; 23. E2F up-regulates RB1[12]; 24. E2F up-regulates c-Myc[13]; 25. E2F up-regulates cyclinE1[14]. 26. E2F drives cell proliferation[15]; 27. ICI increases Cdk6[16–18]; 28. Palbociclib increases cyclinE1[19–24]; 29. AZD decreases cyclinE1, the cyclinE1 increase effect caused by palbociclib and the Cdk6 increase effect caused by ICI[25–28].

## Supplementary Table 1 | Model variables

| Variable name | Description | Half-life |
|---|---|---|
| (1) $E2_{media}$ | E2 concentration in the media | - |
| (2) $E2_{cell}$ | E2 concentration in the cell | - |
| (3) *ER* | Estrogen receptor α | ~4-5h[29] |
| (4) *E2ER* | Estrogen bound estrogen receptor α | ~3-4h[29] |
| (5) *ICIER* | ICI 182,780 bound estrogen receptor | < 3-4h[29] |
| (6) *rescyclinE1palbo* | Variable induced by palbociclib increasing cyclinE1 | - |

| | | |
|---|---|---|
| (7) rescdk6ICI | Variable induced by ICI increasing cdk6 | - |
| (8) *cyclinD1* | cyclinD1 | ~0.4h[30] |
| (9) *cdk4* | Cdk4 | ~5h[31] |
| (10) *cdk6* | Cdk6 | ~5h[31] |
| (11) *cyclinD1cdk4* | CyclinD1 bound Cdk4 | - |
| (12) *cyclinD1cdk6* | CyclinD1 bound Cdk6 | - |
| (13) *cyclinD1cdk4p21* | p21 bound cyclinD1:Cdk4 | - |
| (14) *cyclinD1cdk6p21* | p21 bound cyclinD1:Cdk6 | - |
| (15) *cyclinD1cdk4palbo* | Palbociclib bound cyclinD1:Cdk4 | - |
| (16) *cyclinD1cdk6palbo* | Palbociclib bound cyclinD1:Cdk6 | - |
| (17) *cyclinD1cdk4p21palbo* | Palbociclib bound cyclinD1:Cdk4:p21 | - |
| (18) *cyclinD1cdk6p21palbo* | Palbociclib bound cyclinD1:Cdk6:p21 | - |
| (19) *cMyc* | c-Myc | ~0.3h[32] |
| (20) *p21* | p21 | ~0.3-1h[33] |
| (21) *cyclinE1* | cyclinE1 | ~0.5h[34] |
| (22) *Rb* | Retinoblastoma protein | ~2-3h[35] |
| (23) *pRb* | Hypophosphorylated RB1 (RB1-p) | ~2-3h[35] |
| (24) *ppRb* | Hyperphosphorylated RB1 (RB1-pp) | > 4h[35] |
| (25) *Nalive* | Alive cell number | - |
| (26) *Ndead* | Dead cell number | - |

**Supplementary Table 2 | Model parameter descriptions, values and declaration of fixed or calibrated**

| Parameter name | Description | Value | Fixed/ Calibrated |
|---|---|---|---|
| (1) $k_{diff}$ | Diffusion rate of E2 | 3.37/h | Calibrated |
| (2) $Vol_{1cell}$ | Volume of MCF7 cell | $8\times10^{-5}$mL | Fixed |
| (3) $Vol_{media}$ | Volume of media | 10mL | Fixed |
| (4) $k_{ER}$ | Translation rate of *ER* | 316.28nM/h | Calibrated |
| (5) $kd_{ER}$ | Degradation rate of *ER* | 0.1/h | Fixed |
| (6) $kd_{E2ER}$ | Degradation rate of *E2ER* | 0.3/h | Fixed |
| (7) $kd_{ICIER}$ | Degradation rate of *ICIER* | 4.81/h | Calibrated |
| (8) $kb_{E2ER}$ | Binding rate between *ER* and $E2_{cell}$ | 143.73/(h×nM) | Calibrated |
| (9) $kub_{E2ER}$ | Unbinding rate between *ER* and $E2_{cell}$ | 1.0/h | Fixed |
| (10) $kb_{ICIER}$ | Binding rate between *ICI* and *ER* | 0.3/(h×nM) | Calibrated |
| (11) $kub_{ICIER}$ | Unbinding rate between *ICI* and *ER* | 1.0/h | Fixed |
| (12) $k_{cyclinD1}$ | Translation rate of *cyclinD1* | 11.33nM/h | Calibrated |
| (13) $kd_{cyclinD1}$ | Degradation rate of *cyclinD1* | 1.4/h | Fixed |
| (14) $kb_{cyclinD1cdk46}$ | Binding rate between *cyclinD1* and *cdk46* | $1.7\times10^{4}$ | Calibrated |
| (15) $kub_{cyclinD1cdk46}$ | Unbinding rate between *cyclinD1* and *cdk46* | 1.0/h | Fixed |
| (16) $k_{cyclinD1E2ER}$ | Increasing rate of *cyclinD1* by *E2ER* | 349.12nM/h | Calibrated |

| | | | |
|---|---|---|---|
| (17) $p_{cyclinD1E2ER_1}$ | Parameter 1 of *cyclinD1* increased by *E2ER* | 1592.05nM | Calibrated |
| (18) $p_{cyclinD1E2ER_2}$ | Parameter 2 of *cyclinD1* increased by *E2ER* | 9.03 | Calibrated |
| (19) $k_{cdk6ICI}$ | Increasing rate of *rescdk6ICI* | $6.98\times10^{-5}$nM/h | Calibrated |
| (20) $p_{cdk6ICI_1}$ | Parameter 1 of *rescdk6ICI* increased by *ICI* | 1380.8nM | Calibrated |
| (21) $p_{cdk6ICI_2}$ | Parameter 2 of *rescdk6ICI* increased by *ICI* | 3.25 | Calibrated |
| (22) $kd_{cdk6ICI}$ | Decreasing rate of *rescdk6ICI* | $1.66\times10^{-5}$/h | Calibrated |
| (23) $p_{kdcdk6ICI_1}$ | Parameter 1 of *rescdk6ICI* decreasing | 0.027nM | Calibrated |
| (24) $p_{kdcdk6ICI_2}$ | Parameter 2 of *rescdk6ICI* decreasing | 1.29 | Calibrated |
| (25) $kd_{cdkICI_{AZD}}$ | Decreasing rate of *rescdk6ICI* by *AZD* | $9.02\times10^{-4}$/h | Calibrated |
| (26) $k_{cdk4}$ | Translation rate of *cdk4* | 18.23nM/h | Calibrated |
| (27) $kd_{cdk46}$ | Degradation rate of *cdk46* | 0.1155/h | Fixed |
| (28) $k_{cdk6}$ | Translation rate of *cdk6* | 0.2nM/h | Calibrated |
| (29) $k_{cdk6rescdk6ICI}$ | Increasing rate of *cdk6* by *rescdk6ICI* | 1.45nM/h | Calibrated |
| (30) $p_{cdk6rescdk6ICI_1}$ | Parameter 1 of *cdk6* increased by *rescdk6ICI* | 0.035nM | Calibrated |
| (31) $p_{cdk6rescdk6ICI_2}$ | Parameter 2 of *cdk6* increased by *rescdk6ICI* | 1.93 | Calibrated |
| (32) $kd_{cyclinD1cdk46}$ | Degradation rate of *cyclinD1cdk46* | 0.19/h | Calibrated |
| (33) $kb_{cyclinD1cdk46palbo}$ | Binding rate between *cyclinD1cdk46* and *palbo* | 0.0083/(h×nM) | Calibrated |
| (34) $kub_{cyclinD1cdk46palbo}$ | Unbinding rate between *cyclinD1cdk46* and *palbo* | 1.0/h | Fixed |
| (35) $kb_{cyclinD1cdk46p21}$ | Binding rate between *cyclinD1cdk46* and *p21* | 4.13/(h×nM) | Calibrated |
| (36) $kub_{cyclinD1cdk46p21}$ | Unbinding rate between *cyclinD1cdk46* and *p21* | 1.0/h | Fixed |
| (37) $kb_{cyclinD1cdk46p21palbo}$ | Binding rate between *cyclinD1cdk46p21* and *palbo* | 14.51/(h×nM) | Calibrated |
| (38) $kub_{cyclinD1cdk46p21palbo}$ | Unbinding rate between *cyclinD1cdk46p21* and *palbo* | 1.0/h | Fixed |
| (39) $k_{cMyc}$ | Translation rate of *cMyc* | 13.33nM/h | Calibrated |
| (40) $kd_{cMyc}$ | Degradation rate of *cMyc* | 2.31/h | Fixed |
| (41) $k_{cMycE2ER}$ | Increasing rate of *cMyc* by *E2ER* | 417.36nM/h | Calibrated |
| (42) $p_{cMycE2ER_1}$ | Parameter 1 of *cMyc* increased by *E2ER* | 1811.48nM | Calibrated |
| (43) $p_{cMycE2ER_2}$ | Parameter 2 of *cMyc* increased by *E2ER* | 5.59 | Calibrated |
| (44) $k_{cMycppRb}$ | Increasing rate of *cMyc* by *ppRb* | 59.93nM/h | Calibrated |
| (45) $p_{cMycppRb_1}$ | Parameter 1 of *cMyc* increased by *ppRb* | 18.13nM | Calibrated |
| (46) $p_{cMycppRb_2}$ | Parameter 2 of *cMyc* increased by *ppRb* | 3.76 | Calibrated |
| (47) $k_{p21cMyc}$ | Translation rate of *p21* inhibited by *cMyc* | 11.21nM/h | Calibrated |
| (48) $p_{p21cMyc_1}$ | Parameter 1 of *p21* inhibited by *cMyc* | 6.85nM | Calibrated |
| (49) $p_{p21cMyc_2}$ | Parameter 2 of *p21* inhibited by *cMyc* | 4.24 | Calibrated |
| (50) $kd_{p21}$ | Degradation rate of *p21* | 1.39/h | Fixed |
| (51) $k_{cyclinE1palbo}$ | Increasing rate of *rescyclinE1palbo* | $4.5\times10^{-4}$nM/h | Calibrated |
| (52) $p_{cyclinE1palbo_1}$ | Parameter 1 of *rescyclinE1palbo* increased by *palbo* | 197.66nM | Calibrated |
| (53) $p_{cyclinE1palbo_2}$ | Parameter 2 of *rescyclinE1palbo* increased by *palbo* | 1.19 | Calibrated |
| (54) $kd_{cyclinE1palbo}$ | Decreasing rate of *rescyclinE1palbo* | $3.34\times10^{-4}$/h | Calibrated |
| (55) $p_{kdcyclinE1palbo_1}$ | Parameter 1 of *rescyclinE1palbo* decreasing | 0.14nM | Calibrated |
| (56) $p_{kdcyclinE1palbo_2}$ | Parameter 2 of *rescyclinE1palbo* decreasing | 10 | Calibrated |
| (57) $kd_{cyclinE1palbo_{AZD}}$ | Decreasing rate of *rescyclinE1palbo* by *AZD* | 7.64/h | Calibrated |
| (58) $k_{cyclinE1}$ | Translation rate of *cyclinE1* | 0.39nM/h | Calibrated |
| (59) $kd_{cyclinE1}$ | Degradation rate of *cyclinE1* | 1.39/h | Fixed |

| | | | |
|---|---|---|---|
| (60) $kd_{cyclinE1_{AZD}}$ | Decreasing rate of *cyclinE1* by *AZD* | 0.66/h | Fixed |
| (61) $k_{cyclinE1E2ER}$ | Increasing rate of *cyclinE1* by *E2ER* | 1.39nM/h | Calibrated |
| (62) $p_{cyclinE1E2ER_1}$ | Parameter 1 of *cyclinE1* increased by *E2ER* | 892.32nM | Calibrated |
| (63) $p_{cyclinE1E2ER_2}$ | Parameter 2 of *cyclinE1* increased by *E2ER* | 2.92 | Calibrated |
| (64) $k_{cyclinE1rescyclinE1palbo}$ | Increasing rate of *cyclinE1* by *rescyclinE1palbo* | 5.76nM/h | Calibrated |
| (65) $p_{cyclinE1rescyclinE1palbo_1}$ | Parameter 1 of *cyclinE1* increase by *rescyclinE1palbo* | 1.03nM | Calibrated |
| (66) $p_{cyclinE1rescyclinE1palbo_2}$ | Parameter 2 of *cyclinE1* increase by *rescyclinE1palbo* | 1.36 | Calibrated |
| (67) $k_{Rb}$ | Translation rate of *Rb* | 10.44nM/h | Calibrated |
| (68) $kd_{Rb}$ | Degradation rate of *Rb* | 0.35/h | Fixed |
| (69) $k_{RbppRb}$ | Increasing rate of *Rb* by *ppRb* | 7.13nM/h | Calibrated |
| (70) $p_{RbppRb_1}$ | Parameter 1 of *Rb* increased by *ppRb* | 1.55nM | Calibrated |
| (71) $p_{RbppRb_2}$ | Parameter 2 of *Rb* increased by *ppRb* | 8.18 | Calibrated |
| (72) $k_{RbcyclinD1cdk4}$ | Phosphorylation rate of *Rb* by *cyclinD1cdk4* | 0.25/h | Calibrated |
| (73) $p_{cyclinD1cdk4_1}$ | Parameter 1 of *cyclinD1cdk4* kinase activity | 826.77nM | Calibrated |
| (74) $p_{cyclinD1cdk4_2}$ | Parameter 2 of *cyclinD1cdk4* kinase activity | 0.17 | Calibrated |
| (75) $k_{RbcyclinD1cdk6}$ | Phosphorylation rate of *Rb* by *cyclinD1cdk6* | 1.28/h | Calibrated |
| (76) $p_{cyclinD1cdk6_1}$ | Parameter 1 of *cyclinD1cdk6* kinase activity | 1.91nM | Calibrated |
| (77) $p_{cyclinD1cdk6_2}$ | Parameter 2 of *cyclinD1cdk6* kinase activity | 1.27 | Calibrated |
| (78) $k_{pRbcyclinE1}$ | Phosphorylation rate of *pRb* by *cyclinE1* | 84.2/h | Calibrated |
| (79) $p_{cyclinE1_1}$ | Parameter 1 of *cyclinE1* kinase activity | 1.22nM | Calibrated |
| (80) $p_{cyclinE1_2}$ | Parameter 2 of *cyclinE1* kinase activity | 1.97 | Calibrated |
| (81) $k_{pRbdepho}$ | Dephosphorylation rate of *pRb* | 6.5nM/h | Calibrated |
| (82) $kd_{ppRb}$ | Degradation rate of *ppRb* | 0.05/h | Fixed |
| (83) $k_{ppRbdepho}$ | Dephosphorylation rate of *ppRb* | 21.89nM/h | Calibrated |
| (84) $k_{pro}$ | Basal proliferation rate | 0.0016 | Calibrated |
| (85) $k_{proppRb}$ | Proliferation rate increased by *ppRb* | 0.04 | Calibrated |
| (86) $p_{proppRb_1}$ | Parameter 1 of proliferation rate increased by *ppRb* | 4.27nM | Calibrated |
| (87) $p_{proppRb_2}$ | Parameter 2 of proliferation rate increased by *ppRb* | 3.3 | Calibrated |
| (88) $k_{procyclinE1}$ | Proliferation rate increased by *cyclinE1* | 8.16 | Calibrated |
| (89) $p_{procyclinE1_1}$ | Parameter 1 of proliferation rate increased by *cyclinE1* | 5.27nM | Calibrated |
| (90) $p_{procyclinE1_2}$ | Parameter 2 of proliferation rate increased by *cyclinE1* | 7.41 | Calibrated |
| (91) $k_{carrying}$ | Carrying capacity | 160.31 | Calibrated |
| (92) $k_{death}$ | Death rate | $2.65\times10^{-4}$/hour | Calibrated |
| (93) $k_{lysis}$ | Lysis rate of dead cell | $2.12\times10^{-4}$/hour | Calibrated |
| *E2* | $E2_{media}$ in control condition | 10nM | Fixed |
| *ICI* | Concentration of ICI 182,780 | Treatment dependent | Fixed |
| *palbo* | Concentration of palbociclib | Treatment dependent | Fixed |
| *AZD* | Concentration of AZD1775 | 250nM | Fixed |

## Supplementary Note 2

**Model equations**

$$N = N_{alive} + N_{dead} \quad (1)$$

(1) Total number of cells equals number of alive cells plus number of dead cells

$$\frac{dN_{alive}}{dt} = (k_{pro} + k_{procyclinE1} \times \frac{cyclinE1^{p_{procyclinE1_2}}}{p_{procyclinE1_1}^{p_{procyclinE1_2}} + cyclinE1^{p_{procyclinE1_2}}} + k_{proppRb} \times$$

$$\frac{ppRb^{p_{proppRb_2}}}{p_{proppRb_1}^{p_{proppRb_2}} + ppRb^{p_{proppRb_2}}}) \times N_{alive} \times (1 - \frac{N_{alive}}{k_{carrying}}) \quad (2)$$

$$-k_{death} \times N_{alive} \quad (3)$$

(2) Basal proliferation, increased proliferation by $cyclinE1$ and $ppRb$

(3) Basal death

$$\frac{dN_{dead}}{dt} = k_{death} \times N_{alive} \quad (4)$$

$$-k_{lysis} \times N_{dead} \quad (5)$$

(4) Basal death

(5) Lysis of dead cells

$$\frac{dE2_{media}}{dt} = \frac{k_{diff} \times N \times Vol_{1cell}}{Vol_{media}} \times (E2_{cell} - E2_{media}) \quad (6)$$

(6) E2 concentration changes in media

$$\frac{dE2_{cell}}{dt} = -k_{diff} \times (E2_{cell} - E2_{media}) - \frac{\left(\frac{dN_{alive}}{dt} + \frac{dN_{dead}}{dt}\right)}{N} \times E2_{cell} \quad (7)$$

$$-kb_{E2ER} \times E2_{cell} \times ER + kub_{E2ER} \times E2ER \quad (8)$$

$$-kb_{NSB} \times E2_{cell} + kub_{NSB} \times E2NSB \quad (9)$$

$$+kd_{E2ER} \times E2ER \quad (10)$$

(7) E2 concentration changes in cell

(8) Binding and unbinding between $ER$ and $E2_{cell}$

(9) Binding and unbinding between non-specific binding and $E2_{cell}$ in the cell

(10) Degradation of $E2ER$

$$\frac{dER}{dt} = k_{ER} - kd_{ER} \times ER \quad (11)$$

$$-kb_{E2ER} \times E2_{cell} \times ER + kub_{E2ER} \times E2ER \quad (12)$$

$$-kb_{ICIER} \times ICI \times ER + kub_{ICIER} \times ICIER \quad (13)$$

(11) Translation and degradation of $ER$

(12) Binding and unbinding between $ER$ and $E2_{cell}$

(13) Binding and unbinding between $ER$ and $ICI$

$$\frac{dE2ER}{dt} = -kd_{E2ER} \times E2ER \quad (14)$$

$$+kb_{E2ER} \times E2_{cell} \times ER - kub_{E2ER} \times E2ER \quad (15)$$

(14) Degradation of $E2ER$

(15) Binding and unbinding between $ER$ and $E2_{cell}$

$$\frac{dICIER}{dt} = kb_{ICIER} \times ICI \times ER - kub_{ICIER} \times ICIER \quad (16)$$

$$-kd_{ICIER} \times ICIER \quad (17)$$

(16) Binding and unbinding between $ICI$ and $ER$

(17) Degradation of $ICIER$

$$\frac{dcyclinD1}{dt} = -kd_{cyclinD1} \times cyclinD1 \quad (18)$$

$$+k_{cyclinD1} + k_{cyclinD1E2ER} \times \frac{E2ER^{p_{cyclinD1E2ER_2}}}{p_{cyclinD1E2ER_1}^{p_{cyclinD1E2ER_2}} + E2ER^{p_{cyclinD1E2ER_2}}} \quad (19)$$

$$-kb_{cyclinD1cdk46} \times cyclinD1 \times cdk4 + kub_{cyclinD1cdk46} \times cyclinD1cdk4 \quad (20)$$

$$-kb_{cyclinD1cdk46} \times cyclinD1 \times cdk6 + kub_{cyclinD1cdk46} \times cyclinD1cdk6 \quad (21)$$

(18) Degradation of $cyclinD1$

(19) Basal translation of $cyclinD1$ and the increased by $E2ER$

(20) Binding and unbinding between $cyclinD1$ and $cdk4$

(21) Binding and unbinding between $cyclinD1$ and $cdk6$

$$\frac{drescdk6ICI}{dt} = k_{cdk6ICI} \times \frac{ICI^{p_{cdk6ICI_2}}}{p_{cdk6ICI_1}^{p_{cdk6ICI_2}} + ICI^{p_{cdk6ICI_2}}} \quad (22)$$

$$-kd_{cdk6ICI} \times \frac{rescdk6ICI^{p_{kdcdk6ICI_2}}}{p_{kdcdk6ICI_1}^{p_{kdcdk6ICI_2}} + rescdk6ICI^{p_{kdcdk6ICI_2}}} \quad (23)$$

$$-kd_{cdk6ICI_{AZD}} \times rescdk6ICI \times sign(AZD) \quad (24)$$

(22) Increasing $rescdk6ICI$ by $ICI$

(23) Decreasing $rescdk6ICI$

(24) Decreasing $rescdk6ICI$ by $AZD$

$$\frac{dcdk4}{dt} = k_{cdk4} - kd_{cdk46} \times cdk4 \quad (25)$$

$$-kb_{cyclinD1cdk46} \times cyclinD1 \times cdk4 + kub_{cyclinD1cdk46} \times cyclinD1cdk4 \quad (26)$$

(25) Translation and degradation of $cdk4$

(26) Binding and unbinding between $cyclinD1$ and $cdk4$

$$\frac{dcdk6}{dt} = k_{cdk6} - kd_{cdk46} \times cdk6 \quad (27)$$

$$-kb_{cyclinD1cdk46} \times cyclinD1 \times cdk6 + kub_{cyclinD1cdk46} \times cyclinD1cdk6 \quad (28)$$

$$+k_{cdk6rescdk6ICI} \times \frac{rescdk6ICI^{p_{cdk6rescdk6ICI_2}}}{p_{cdk6rescdk6ICI_1}^{p_{cdk6rescdk6ICI_2}} + rescdk6ICI^{p_{cdk6rescdk6ICI_2}}} \quad (29)$$

(27) Translation and degradation of $cdk6$

(28) Binding and unbinding between $cyclinD1$ and $cdk6$

(29) Increasing $cdk6$ by $rescdk6ICI$

$$\frac{dcyclinD1cdk4}{dt} = -kd_{cyclinD1cdk46} \times cyclinD1cdk4 \quad (30)$$

$$+kb_{cyclinD1cdk46} \times cyclinD1 \times cdk4 - kub_{cyclinD1cdk46} \times cyclinD1cdk4 \quad (31)$$

$$-kb_{cyclinD1cdk46p21} \times cyclinD1cdk4 \times p21 + kub_{cyclinD1cdk46p21} \times cyclinD1cdk4p21 \quad (32)$$

$$-kb_{cyclinD1cdk46palbo} \times cyclinD1cdk4 \times palbo + kub_{cyclinD1cdk46palbo} \times cyclinD1cdk4palbo$$

(33)

(30) Degradation of $cyclinD1cdk4$

(31) Binding and unbinding between $cyclinD1$ and $cdk4$

(32) Binding and unbinding between $p21$ and $cyclinD1cdk4$

(33) Binding and unbinding between $palbo$ and $cyclinD1cdk4$

$$\frac{dcyclinD1cdk6}{dt} = -kd_{cyclinD1cdk46} \times cyclinD1cdk6 \quad (34)$$

$$+kb_{cyclinD1cdk46} \times cyclinD1 \times cdk6 - kub_{cyclinD1cdk46} \times cyclinD1cdk6 \quad (35)$$

$$-kb_{cyclinD1cdk46p21} \times cyclinD1cdk6 \times p21 + kub_{cyclinD1cdk46p21} \times cyclinD1cdk6p21 \quad (36)$$

$$-kb_{cyclinD1cdk46palbo} \times cyclinD1cdk6 \times palbo + kub_{cyclinD1cdk46palbo} \times cyclinD1cdk6dpalbo \quad (37)$$

(34) Degradation of $cyclinD1cdk6$

(35) Binding and unbinding between $cyclinD1$ and $cdk6$

(36) Binding and unbinding between $p21$ and $cyclinD1cdk6$

(37) Binding and unbinding between $palbo$ and $cyclinD1cdk6$

$$\frac{dcyclinD1cdk4p21}{dt} = -kd_{cdk46} \times cyclinD1cdk4p21 \quad (38)$$

$$+kb_{cyclinD1cdk46p21} \times cyclinD1cdk4 \times p21 - kub_{cyclinD1cdk46p21} \times cyclinD1cdk4p21 \quad (39)$$

$$-kb_{cyclinD1cdk46p21palbo} \times cyclinD1cdk4p21 \times palbo + kub_{cyclinD1cdk46p21palbo} \times cyclinD1cdk4p21palbo \quad (40)$$

(38) Degradation of $cyclinD1cdk4p21$

(39) Binding and unbinding between $p21$ and $cyclinD1cdk4$

(40) Binding and unbinding between $palbo$ and $cyclinD1cdk4p21$

$$\frac{dcyclinD1cdk6p21}{dt} = -kd_{cdk46} \times cyclinD1cdk6p21 \quad (41)$$

$$+kb_{cyclinD1cdk46p21} \times cyclinD1cdk6 \times p21 - kub_{cyclinD1cdk46p21} \times cyclinD1cdk6p21 \quad (42)$$

$$-kb_{cyclinD1cdk46p21palbo} \times cyclinD1cdk6p21 \times palbo + kub_{cyclinD1cdk46p21palbo} \times cyclinD1cdk6p21palbo \quad (43)$$

(41) Degradation of $cyclinD1cdk6p21$

(42) Binding and unbinding between $p21$ and $cyclinD1cdk6$

(43) Binding and unbinding between $palbo$ and $cyclinD1cdk6p21$

$$\frac{dcyclinD1cdk4palbo}{dt} = -kd_{cyclinD1cdk46} \times cyclinD1cdk4palbo \quad (44)$$

$$+kb_{cyclinD1cdk46palbo} \times cyclinD1cdk4 \times palbo - kub_{cyclinD1cdk46palbo} \times cyclinD1cdk4palbo \quad (45)$$

(44) Degradation of $cyclinD1cdk4palbo$

(45) Binding and unbinding between $palbo$ and $cyclinD1cdk4$

$$\frac{dcyclinD1cdk6palbo}{dt} = -kd_{cyclinD1cdk46} \times cyclinD1cdk6palbo \quad (46)$$

$$+kb_{cyclinD1cdk46palbo} \times cyclinD1cdk6 \times palbo - kub_{cyclinD1cdk46palbo} \times cyclinD1cdk6palbo \quad (47)$$

(46) Degradation of $cyclinD1cdk6palbo$

(47) Binding and unbinding between $palbo$ and $cyclinD1cdk6$

$$\frac{dcyclinD1cdk4p21palbo}{dt} = -kd_{cdk46} \times cyclinD1cdk4p21palbo \quad (48)$$

$$+kb_{cyclinD1cdk46p21palbo} \times cyclinD1cdk4p21 \times palbo - kub_{cyclinD1cdk46p21palbo} \times cyclinD1cdk4p21palbo \quad (49)$$

(48) Degradation of $cyclinD1cdk4p21palbo$

(49) Binding and unbinding between $palbo$ and $cyclinD1cdk4p21$

$$\frac{dcyclinD1cdk6p21palbo}{dt} = -kd_{cdk46} \times cyclinD1cdk6p21palbo \quad (50)$$

$$+kb_{cyclinD1cdk46p21palbo} \times cyclinD1cdk6p21 \times palbo - kub_{cyclinD1cdk46p21palbo} \times cyclinD1cdk6p21palbo \quad (51)$$

(50) Degradation of $cyclinD1cdk46p21palbo$

(51) Binding and unbinding between $palbo$ and $cyclinD1cdk46p21$

$$\frac{dcMyc}{dt} = k_{cMyc} - kd_{cMyc} \times cMyc \quad (52)$$

$$+k_{cMycE2ER} \times \frac{E2ER^{p_{cMycE2ER_2}}}{p_{cMycE2ER_1}^{p_{cMycE2ER_2}} + E2ER^{p_{cMycE2ER_2}}} + k_{cMycppRb} \times \frac{ppRb^{p_{cMycppRb_2}}}{p_{cMycppRb_1}^{p_{cMycppRb_2}} + ppRb^{p_{cMycppRb_2}}} \quad (53)$$

(52) Basal translation of $cMyc$ and degradation of $cMyc$

(53) Increase of $cMyc$ by $E2ER$ and $ppRb$

$$\frac{dp21}{dt} = k_{p21cMyc} \times \frac{p_{p21cMyc_1}^{p_{p21cMyc_2}}}{p_{p21cMyc_1}^{p_{p21cMyc_2}} + cMyc^{p_{p21cMyc_2}}} - kd_{p21} \times p21 \quad (54)$$

$$-kb_{cyclinD1cdk46p21} \times cyclinD1cdk4 \times p21 + kub_{cyclinD1cdk46p21} \times cyclinD1cdk4p21 \quad (55)$$

$$-kb_{cyclinD1cdk46p21} \times cyclinD1cdk6 \times p21 + kub_{cyclinD1cdk46p21} \times cyclinD1cdk6p21 \quad (56)$$

(54) Inhibited translation of $p21$ by $cMyc$ and degradation of $p21$

(55) Binding and unbinding between $p21$ and $cyclinD1cdk4$

(56) Binding and unbinding between $p21$ and $cyclinD1cdk6$

$$\frac{drescyclinE1palbo}{dt} = k_{cyclinE1palbo} \times \frac{palbo^{p_{cyclinE1palbo_2}}}{p_{cyclinE1palbo_1}^{cyclinE1palbo_2} + palbo^{p_{cyclinE1palbo_2}}} \quad (57)$$

$$-kd_{cyclinE1palbo} \times \frac{rescyclinE1palbo^{p_{kdcyclinE1palbo_2}}}{p_{kdcyclinE1palbo_1}^{p_{kdcyclinE1palbo_2}} + rescyclinE1palbo^{p_{kdcyclinE1palbo_2}}} \quad (58)$$

$$-kd_{cyclinE1palbo_{AZD}} \times rescyclinE1palbo \times sign(AZD) \quad (59)$$

(57) Increasing $rescyclinE1palbo$ by $palbo$

(58) Decreasing $rescyclinE1palbo$

(59) Decreasing $rescyclinE1palbo$ by $AZD$

$$\frac{dcyclinE1}{dt} = -kd_{cyclinE1} \times cyclinE1 \quad (60)$$

$$+k_{cyclinE1} + k_{cyclinE1E2ER} \frac{E2ER^{p_{cyclinE1E2ER_2}}}{p_{cyclinE1E2ER_1}^{p_{cyclinE1E2ER_2}} + E2ER^{p_{cyclinE1E2ER_2}}} \quad (61)$$

$$+k_{cyclinE1rescyclinE1palbo} \times \frac{rescyclinE1palbo^{p_{cyclinE1rescyclinE1palbo_2}}}{p_{cyclinE1rescyclinE1palbo_1}^{p_{cyclinE1rescyclinE1palbo_2}} + rescyclinE1palbo^{p_{cyclinE1rescyclinE1palbo_2}}}$$

(62)

$$-kd_{cyclinE1_{AZD}} \times cyclinE1 \times sign(AZD) \quad (63)$$

(60) Degradation of $cyclinE1$

(61) Basal translation of $cyclinE1$ and increased by $E2ER$

(62) Increasing $cyclinE1$ by $rescyclinE1palbo$

(63) Decreasing $cyclinE1$ by $AZD$

$$\frac{dRb}{dt} = k_{Rb} - kd_{Rb} \times Rb \tag{64}$$

$$+k_{RbppRb} \times \frac{ppRb^{p_{RbppRb_2}}}{p_{RbppRb_1}^{p_{RbppRb_2}} + ppRb^{p_{RbppRb_2}}} \tag{65}$$

$$-k_{RbcyclinD1cdk4} \times \frac{cyclinD1cdk4^{p_{cyclinD1cdk4_2}}}{p_{cyclinD1cdk4_1}^{p_{cyclinD1cdk4_2}} + cyclinD1cdk4^{p_{cyclinD1cdk4_2}}} \times Rb \tag{66}$$

$$-k_{RbcyclinD1cdk6} \times \frac{cyclinD1cdk6^{p_{cyclinD1cdk6_2}}}{p_{cyclinD1cdk6_1}^{p_{cyclinD1cdk6_2}} + cyclinD1cdk6^{p_{cyclinD1cdk6_2}}} \times Rb \tag{67}$$

$$+k_{pRbdepho} \times pRb \tag{68}$$

(64) Basal translation and degradation of $Rb$

(65) Increasing $Rb$ by $ppRb$

(66) Phosphorylation of $Rb$ by $cyclinD1cdk4$

(67) Phosphorylation of $Rb$ by $cyclinD1cdk6$

(68) Dephosphorylation of $pRb$

$$\frac{dpRb}{dt} = -kd_{Rb} \times pRb \tag{69}$$

$$+k_{RbcyclinD1cdk4} \times \frac{cyclinD1cdk4^{p_{cyclinD1cdk4_2}}}{p_{cyclinD1cdk4_1}^{p_{cyclinD1cdk4_2}} + cyclinD1cdk4^{p_{cyclinD1cdk4_2}}} \times Rb \tag{70}$$

$$+k_{RbcyclinD1cdk6} \times \frac{cyclinD1cdk6^{p_{cyclinD1cdk6_2}}}{p_{cyclinD1cdk6_1}^{p_{cyclinD1cdk6_2}} + cyclinD1cdk6^{p_{cyclinD1cdk6_2}}} \times Rb \tag{71}$$

$$-k_{pRbdepho} \times pRb \tag{72}$$

$$-k_{pRbcyclinE1} \times \frac{cyclinE1^{p_{cyclinE1_2}}}{p_{cyclinE1_1}^{p_{cyclinE1_2}} + cyclinE1^{p_{cyclinE1_2}}} \times pRb \tag{73}$$

$$+k_{ppRbdepho} \times ppRb \tag{74}$$

(69) Degradation of $pRb$

(70) Phosphorylation of $Rb$ by $cyclinD1cdk4$

(71) Phosphorylation of $Rb$ by $cyclinD1cdk6$

(72) Dephosphorylation of $pRb$

(73) Phosphorylation of $pRb$ by $cyclinE$

(74) Dephosphorylation of $ppRb$

$$\frac{dppRb}{dt} = -kd_{ppRb} \times ppRb \quad (75)$$

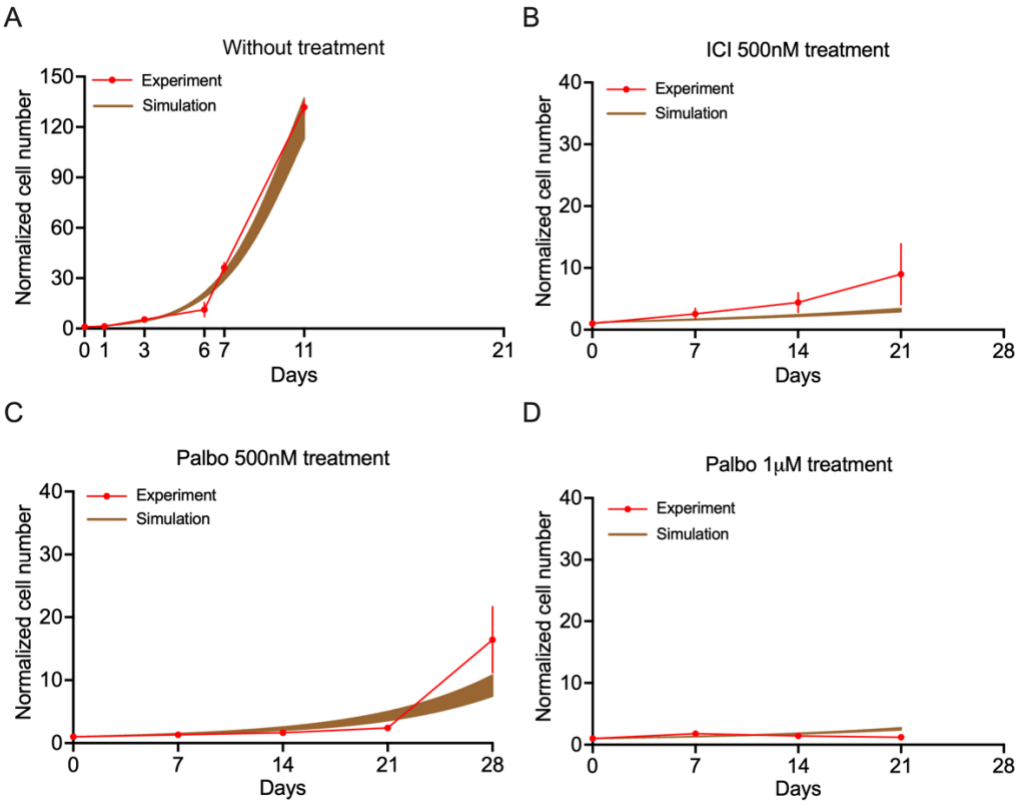
$$+k_{pRbcyclinE1} \times \frac{cyclinE1^{p_{cyclinE1_2}}}{p_{cyclinE1_1}^{p_{cyclinE1_2}} + cyclinE1^{p_{cyclinE1_2}}} \times pRb \quad (76)$$

$$-k_{ppRbdepho} \times ppRb \quad (77)$$

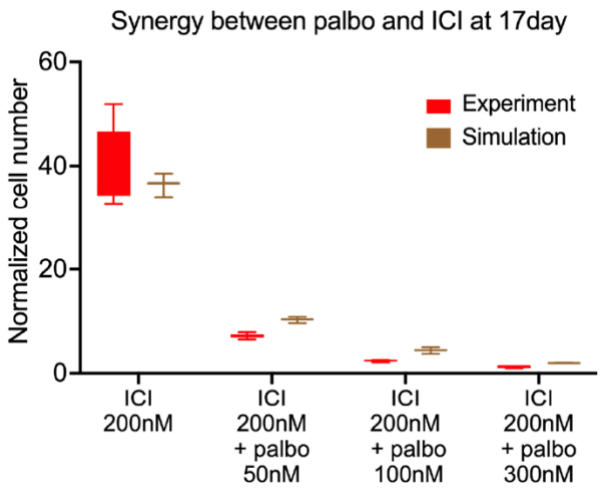
(75) Degradation of $ppRb$

(76) Phosphorylation of $pRb$ by $cyclinE$

(77) Dephosphorylation of $ppRb$




**Supplementary Figure 1. Mathematical model simulation compared to proliferation data for various treatments.** (A) Without treatment (n = 3) for 11 days. The experimental data are shown in red and the simulation results are shown in brown (the shaded regions encompass the entire range of simulations within the cohort). (B) 500nM ICI treatment (n = 3) for 21 days. (C) 500nM Palbociclib treatment (n = 3) for 28 days. (D) 1μM Palbociclib treatment (n = 3) for 21 days. Palbo: palbociclib.




**Supplementary Figure 2. Boxplot of the model simulations and experimental verifications of normalized cell number showing the synergism between palbociclib and ICI.** The experimental results are shown in red. The simulation results are shown in brown from all cohort simulation results. The bottom and top lines on each box are the 25$^{th}$ and 75$^{th}$ percentiles, respectively. This synergism is thoroughly discussed in previous work[36].

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