**Table S1. Reactions and reaction rates of the EGFR-c-MET-PYK2 network model**

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| --- | --- | --- |
|  | **Reaction** | **Reaction rates** |
| v1 | EGFR → pEGFR | kc1\*(EGF/(1+Gefitinib/Ki1)+caEGF)\*EGFR/(Km1+EGFR) |
| v2 | pEGFR → EGFR | (Vmax2+kc2\*aPTP)\*pEGFR/(Km2+pEGFR) |
| v3 | EGFR → EGFRub | (Vmax3+kc3\*pCbl)\*EGFR/(Km3+EGFR)\*Ki3a/(Ki3a+PYK2tot/(1+PF396/Ki3b)) |
| v4 | EGFRub → EGFR | Vmax4\*EGFRub/(Km4+EGFRub) |
| v5 | ∅ → PYK2m | Vs5 + Vmax5\*pSTAT3/(Km5+pSTAT3) |
| v6 | PYK2m → ∅ | kdeg6\*PYK2m |
| v7 | PYK2m → PYK2 | Vmax7\*PYK2m/(Km7+PYK2m) |
| v8 | PYK2 → ∅ | kdeg8\*PYK2 |
| v9 | PYK2 → pPYK2 | (kc9a\*pEGFR+kc9b\*pcMET/(1+EMD/Ki9))\*PYK2/(Km9+PYK2) |
| v10 | pPYK2 → PYK2 | (Vmax10+kc10\*aPTP)\*pPYK2/(Km10+pPYK2) |
| v11 | STAT3→ pSTAT3 | kc11\*(pPYK2/(1+PF396/Ki3b))\*STAT3/(Km11+STAT3) |
| v12 | pSTAT3→ STAT3 | (Vmax12+kc12\*aPTP)\*pSTAT3/(Km12+pSTAT3) |
| v13 | ∅ → cMETm | Vs13 + Vmax13\*pSTAT3/(Km13+pSTAT3) |
| v14 | cMETm→ ∅ | kdeg14\*cMETm |
| v15 | cMETm → cMET | Vmax15\*cMETm/(Km15+cMETm) |
| v16 | cMET → ∅ | (kdeg16+kc16\*pCbl)\*cMET/(Km16+cMET) |
| v17 | cMET → pcMET | (kc17\*HGF+caHGF)\*cMET/(Km17+cMET) |
| v18 | pcMET → cMET | Vmax18\*pcMET/(Km18+pcMET) |
| v19 | Cbl → pCbl | kc19\*pEGFR\*Cbl/(Km19+Cbl) |
| v20 | pCbl → Cbl | (Vmax20+kc20\*aPTP)\*pCbl/(Km20+pCbl) |
| v21 | PTP → aPTP | kc21\*pEGFR\*PTP/(Km21+PTP) |
| v22 | aPTP → PTP | Vmax22\*aPTP/(Km22+aPTP) |
| v23 | ERK → pERK | (kc23a\*pcMET/(1+EMD/Ki23)+kc23b\*pEGFR)\*ERK/(Km23+ERK) |
| v24 | pERK → ERK | Vmax24\*pERK/(Km24+pERK) |
| v25 | STAT3 + Stattic  ↔ STAT3uStattic | ka25\*STAT3\*Stattic - kd25\*STAT3uStattic |

*Footnote:* The effects of the inhibitorsGefitinib, PF396 and EMD were modelled by incorporating into the rate equations v1, v3 & v11 and v9 & v23, respectively. We assumed that Gefitinib inhibits EGFR phosphorylation since Gefitinib effectively inhibits all EGFR tyrosine phosphorylation sites in both high and low EGFR-expressing cell lines [1]. Parameter Ki1 represents the inhibition strength exerted by Gefitinib on EGFR. PYK2 inhibitor PF396 is a kinase inhibitor that blocks the transferring a phosphate group to a target protein from ATP, and it directly binds to the active site of PYK2 and inhibits its function [2]. Thus, PF396 was assumed to inhibit the kinase activity of PYK2, and its strength is indicated by the parameter Ki3b (while Ki3a is a kinetic parameter value associated with PYK2 inhibition of EGFR ubiquitination). We assumed that the c-Met inhibitor EMD-1214063 (EMD) is an ATP-competitive small molecule that inhibits c-Met phosphorylation of target substrates [3,4]. Ki9 and Ki23 represent inhibition coefficients of the c-Met inhibitor towards PYK2 and ERK as c-Met substrates, respectively. Furthermore, the effect of the STAT inhibitor, Stattic was modelled according to a reversible drug-target binding reaction (as in v25) since Stattic was reported to selectively inhibit dimerization and activation of STAT3 [5]. We assumed that the STAT3 inhibitor directly bind and form an inhibition complex and Ka25 and Kd25 denotes the binding coefficients. The binding affinity (kd25/ka25) was estimated 92 µM based on the previous experimental observation [5]. They displayed the STAT3 activation was fully suppressed around 200-250µM and the half-maximal concentration was about 100µM. Ki3a was estimated based on the time-course training data shown in Fig 1c-g. Ki3b were estimated based on the PYK2 perturbation data in Fig 1o-r. Ki9 and Ki23 were estimated using c-Met inhibition data used for training now shown in Fig. S1. As we did not use Gefitinib related data to train the model, Ki1 was set to a fixed value. Note that variation of Gefitinib- and PF396- associated parameters (Ki1 and Ki3b) does not have any significant influence on the CI scores of drug synergy (Fig. S5).

**SUPPLEMENTARY REFERENCE**

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