

```

<?xml version="1.0" encoding="UTF-8"?>

<sbml xmlns="http://www.sbml.org/sbml/level2" level="2" version="1">

  <model name="CDK4/6Inhibition-CellCycleandMitogenicPathways">

    <listOfCompartments>

      <compartment id="rootCompartment" name="rootCompartment"
spatialDimensions="3" size="1" constant="true"/>

    </listOfCompartments>

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hasOnlySubstanceUnits="true" boundaryCondition="false" constant="false"/>

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      <species id="PIP3" name="PIP3" compartment="rootCompartment"
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      <species id="aPDK1" name="aPDK1" compartment="rootCompartment"
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  <assignmentRule variable="IR_Total">
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply>
        <plus/>
        <ci> IR </ci>
        <ci> pIR </ci>
      </apply>
    </math>
  </assignmentRule>
  <assignmentRule variable="PI3K_Total">
    <math xmlns="http://www.w3.org/1998/Math/MathML">
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        <plus/>
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        <ci> pPI3K </ci>
      </apply>
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  </assignmentRule>
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        <plus/>

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    <ci> PIP2 </ci>

    <ci> PIP3 </ci>

  </apply>

</math>

</assignmentRule>

<assignmentRule variable="PDK1_Total">

  <math xmlns="http://www.w3.org/1998/Math/MathML">

    <apply>

      <plus/>

      <ci> PDK1 </ci>

      <ci> aPDK1 </ci>

    </apply>

  </math>

</assignmentRule>

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    <apply>

      <plus/>

      <ci> mTORC2 </ci>

      <ci> amTORC2 </ci>

    </apply>

  </math>

</assignmentRule>

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  <math xmlns="http://www.w3.org/1998/Math/MathML">

    <apply>

      <plus/>

      <ci> AKT </ci>

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    <ci> pAKT308 </ci>

    <ci> ppAKT308473 </ci>

  </apply>

</math>

</assignmentRule>

<assignmentRule variable="mTORC1_Total">

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      <plus/>

      <ci> mTORC1 </ci>

      <ci> amTORC1 </ci>

    </apply>

  </math>

</assignmentRule>

<assignmentRule variable="S6K_Total">

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    <apply>

      <plus/>

      <ci> S6K </ci>

      <ci> pS6K </ci>

    </apply>

  </math>

</assignmentRule>

<assignmentRule variable="FGFR_Total">

  <math xmlns="http://www.w3.org/1998/Math/MathML">

    <apply>

      <plus/>

      <ci> FGFR </ci>

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    <ci> pFGFR </ci>

  </apply>

</math>

</assignmentRule>

<assignmentRule variable="Ras_Total">

  <math xmlns="http://www.w3.org/1998/Math/MathML">

    <apply>

      <plus/>

      <ci> Ras </ci>

      <ci> aRas </ci>

    </apply>

  </math>

</assignmentRule>

<assignmentRule variable="Raf_Total">

  <math xmlns="http://www.w3.org/1998/Math/MathML">

    <apply>

      <plus/>

      <ci> Raf </ci>

      <ci> aRaf </ci>

    </apply>

  </math>

</assignmentRule>

<assignmentRule variable="MEK_Total">

  <math xmlns="http://www.w3.org/1998/Math/MathML">

    <apply>

      <plus/>

      <ci> MEK </ci>

      <ci> pMEK </ci>

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    </apply>
  </math>
</assignmentRule>
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      <ci> pERK </ci>
    </apply>
  </math>
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      <ci> aERa </ci>
    </apply>
  </math>
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      <ci> GSK3b </ci>
      <ci> pGSK3b </ci>
    </apply>

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</math>

</assignmentRule>

<assignmentRule variable="FOXO3_Total">

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<apply>

<plus/>

<ci> FOXO3 </ci>

<ci> pFOXO3 </ci>

</apply>

</math>

</assignmentRule>

<assignmentRule variable="CDK46_Total">

<math xmlns="http://www.w3.org/1998/Math/MathML">

<apply>

<plus/>

<ci> CDK46 </ci>

<ci> CDK46cycD </ci>

</apply>

</math>

</assignmentRule>

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<apply>

<plus/>

<ci> CDK2 </ci>

<ci> CDK2cycE </ci>

<ci> CDK2cycA </ci>

</apply>

</math>

</assignmentRule>

<assignmentRule variable="p2127_Total">

<math xmlns="http://www.w3.org/1998/Math/MathML">

<apply>

<plus/>

<ci> p2127 </ci>

<ci> pp2127 </ci>

</apply>

</math>

</assignmentRule>

<assignmentRule variable="Rb_Total">

<math xmlns="http://www.w3.org/1998/Math/MathML">

<apply>

<plus/>

<ci> Rb </ci>

<ci> pRb </ci>

<ci> pppRb </ci>

</apply>

</math>

</assignmentRule>

<assignmentRule variable="Ins">

<math xmlns="http://www.w3.org/1998/Math/MathML">

<apply>

<times/>

<ci> Ins_0 </ci>

<piecewise>

<piece>

```

    <cn type="integer"> 1 </cn>

    <apply>

      <geq/>

      <csymbol encoding="text"
definitionURL="http://www.sbml.org/sbml/symbols/time"> time </csymbol>

      <ci> Ins_on </ci>

    </apply>

  </piece>

</otherwise>

  <cn type="integer"> 0 </cn>

</otherwise>

</piecewise>

</apply>

</math>

</assignmentRule>

<assignmentRule variable="FGF">

  <math xmlns="http://www.w3.org/1998/Math/MathML">

    <apply>

      <times/>

      <ci> FGF_0 </ci>

      <piecewise>

        <piece>

          <cn type="integer"> 1 </cn>

          <apply>

            <geq/>

            <csymbol encoding="text"
definitionURL="http://www.sbml.org/sbml/symbols/time"> time </csymbol>

            <ci> FGF_on </ci>

          </apply>

```

```

    </piece>
    <otherwise>
      <cn type="integer"> 0 </cn>
    </otherwise>
  </piecewise>
</apply>
</math>
</assignmentRule>
<assignmentRule variable="Est">
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <times/>
      <ci> Est_0 </ci>
      <piecewise>
        <piece>
          <cn type="integer"> 1 </cn>
          <apply>
            <geq/>
            <csymbol encoding="text"
definitionURL="http://www.sbml.org/sbml/symbols/time"> time </csymbol>
            <ci> Est_on </ci>
          </apply>
        </piece>
        <otherwise>
          <cn type="integer"> 0 </cn>
        </otherwise>
      </piecewise>
    </apply>
  </math>

```

```

</math>
</assignmentRule>
<assignmentRule variable="Ei_0">
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <times/>
      <ci> Ei </ci>
      <piecewise>
        <piece>
          <cn type="integer"> 1 </cn>
          <apply>
            <geq/>
            <csymbol encoding="text"
definitionURL="http://www.sbml.org/sbml/symbols/time"> time </csymbol>
            <ci> Ei_on </ci>
          </apply>
        </piece>
        <otherwise>
          <cn type="integer"> 0 </cn>
        </otherwise>
      </piecewise>
    </apply>
  </math>
</assignmentRule>
<assignmentRule variable="CDK46i_0">
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <times/>

```

```

    <ci> CDK46i </ci>

    <piecewise>

      <piece>

        <cn type="integer"> 1 </cn>

        <apply>

          <geq/>

          <csymbol encoding="text"
definitionURL="http://www.sbml.org/sbml/symbols/time"> time </csymbol>

            <ci> CDK46i_on </ci>

          </apply>

        </piece>

        <otherwise>

          <cn type="integer"> 0 </cn>

        </otherwise>

      </piecewise>

    </apply>

  </math>

</assignmentRule>

</listOfRules>

<listOfReactions>

  <reaction id="R1" name="R1" reversible="true">

    <listOfReactants>

      <speciesReference species="IR" stoichiometry="1"/>

    </listOfReactants>

    <listOfProducts>

      <speciesReference species="pIR" stoichiometry="1"/>

    </listOfProducts>

    <kineticLaw>

```

```

<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply>
    <minus/>
    <apply>
      <times/>
      <ci> kc1f1 </ci>
      <ci> Ins </ci>
      <ci> IR </ci>
    </apply>
  </apply>
  <times/>
  <ci> Vmax1r1 </ci>
  <ci> pIR </ci>
</apply>
</math>
</kineticLaw>
</reaction>
<reaction id="R2" name="R2" reversible="true">
  <listOfReactants>
    <speciesReference species="PI3K" stoichiometry="1"/>
  </listOfReactants>
  <listOfProducts>
    <speciesReference species="pPI3K" stoichiometry="1"/>
  </listOfProducts>
  <listOfModifiers>
    <modifierSpeciesReference species="pFGFR"/>
    <modifierSpeciesReference species="pIR"/>
  </listOfModifiers>
</reaction>

```

<modifierSpeciesReference species="pS6K"/>

</listOfModifiers>

<kineticLaw>

<math xmlns="http://www.w3.org/1998/Math/MathML">

<apply>

<minus/>

<apply>

<plus/>

<apply>

<divide/>

<apply>

<times/>

<ci> kc2f1 </ci>

<ci> pIR </ci>

<ci> PI3K </ci>

</apply>

<apply>

<plus/>

<cn type="integer"> 1 </cn>

<apply>

<divide/>

<ci> pS6K </ci>

<ci> Ki2 </ci>

</apply>

</apply>

</apply>

<apply>

<times/>

```

      <ci> kc2f2 </ci>

      <ci> pFGFR </ci>

      <ci> PI3K </ci>

    </apply>

  </apply>

  <apply>

    <times/>

    <ci> Vmax2r1 </ci>

    <ci> pPI3K </ci>

  </apply>

</apply>

</math>

</kineticLaw>

</reaction>

<reaction id="R3" name="R3" reversible="true">

  <listOfReactants>

    <speciesReference species="PIP2" stoichiometry="1"/>

  </listOfReactants>

  <listOfProducts>

    <speciesReference species="PIP3" stoichiometry="1"/>

  </listOfProducts>

  <listOfModifiers>

    <modifierSpeciesReference species="pPI3K"/>

  </listOfModifiers>

  <kineticLaw>

    <math xmlns="http://www.w3.org/1998/Math/MathML">

      <apply>

        <minus/>

```

<apply>

<times/>

<ci> kc3f1 </ci>

<ci> pPI3K </ci>

<ci> PIP2 </ci>

</apply>

<apply>

<times/>

<apply>

<plus/>

<ci> Vmax3r1 </ci>

<apply>

<times/>

<ci> kc3r1 </ci>

<ci> PTEN </ci>

</apply>

</apply>

<ci> PIP3 </ci>

</apply>

</apply>

</math>

</kineticLaw>

</reaction>

<reaction id="R4" name="R4" reversible="true">

<listOfReactants>

<speciesReference species="PDK1" stoichiometry="1"/>

</listOfReactants>

<listOfProducts>

```

    <speciesReference species="aPDK1" stoichiometry="1"/>
  </listOfProducts>
  <listOfModifiers>
    <modifierSpeciesReference species="PIP3"/>
  </listOfModifiers>
  <kineticLaw>
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply>
        <minus/>
        <apply>
          <times/>
          <ci> kc4f1 </ci>
          <ci> PIP3 </ci>
          <ci> PDK1 </ci>
        </apply>
        <apply>
          <times/>
          <ci> Vmax4r1 </ci>
          <ci> aPDK1 </ci>
        </apply>
      </apply>
    </math>
  </kineticLaw>
</reaction>
<reaction id="R5" name="R5" reversible="true">
  <listOfReactants>
    <speciesReference species="mTORC2" stoichiometry="1"/>
  </listOfReactants>

```

```

<listOfProducts>

  <speciesReference species="amTORC2" stoichiometry="1"/>

</listOfProducts>

<listOfModifiers>

  <modifierSpeciesReference species="PIP3"/>

  <modifierSpeciesReference species="pppRb"/>

</listOfModifiers>

<kineticLaw>

  <math xmlns="http://www.w3.org/1998/Math/MathML">

    <apply>

      <minus/>

      <apply>

        <divide/>

        <apply>

          <times/>

          <ci> kc5f1 </ci>

          <ci> PIP3 </ci>

          <ci> mTORC2 </ci>

        </apply>

        <apply>

          <plus/>

          <cn type="integer"> 1 </cn>

        </apply>

        <divide/>

        <ci> pppRb </ci>

        <ci> Ki5 </ci>

      </apply>

    </apply>

  </math>
</kineticLaw>

```

```

    </apply>
  <apply>
    <times/>
    <ci> Vmax5r1 </ci>
    <ci> amTORC2 </ci>
  </apply>
</apply>
</math>
</kineticLaw>
</reaction>
<reaction id="R6" name="R6" reversible="true">
  <listOfReactants>
    <speciesReference species="AKT" stoichiometry="1"/>
  </listOfReactants>
  <listOfProducts>
    <speciesReference species="pAKT308" stoichiometry="1"/>
  </listOfProducts>
  <listOfModifiers>
    <modifierSpeciesReference species="aPDK1"/>
  </listOfModifiers>
  <kineticLaw>
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply>
        <minus/>
        <apply>
          <times/>
          <ci> kc6f1 </ci>
          <ci> aPDK1 </ci>

```

```

      <ci> AKT </ci>
    </apply>
  <apply>
    <times/>
    <ci> Vmax6r1 </ci>
    <ci> pAKT308 </ci>
  </apply>
</apply>
</math>
</kineticLaw>
</reaction>
<reaction id="R7" name="R7" reversible="true">
  <listOfReactants>
    <speciesReference species="pAKT308" stoichiometry="1"/>
  </listOfReactants>
  <listOfProducts>
    <speciesReference species="ppAKT308473" stoichiometry="1"/>
  </listOfProducts>
  <listOfModifiers>
    <modifierSpeciesReference species="CDK2cycA"/>
    <modifierSpeciesReference species="amTORC2"/>
  </listOfModifiers>
  <kineticLaw>
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply>
        <minus/>
        <apply>
          <times/>

```

```

    <ci> kc7f1 </ci>

    <ci> amTORC2 </ci>

    <ci> pAKT308 </ci>

    <apply>

      <plus/>

      <cn type="integer"> 1 </cn>

      <apply>

        <times/>

        <ci> alpha7 </ci>

        <ci> CDK2cycA </ci>

      </apply>

    </apply>

  </apply>

</math>

</kineticLaw>

</reaction>

<reaction id="R8" name="R8" reversible="true">

  <listOfReactants>

    <speciesReference species="mTORC1" stoichiometry="1"/>

  </listOfReactants>

  <listOfProducts>

    <speciesReference species="amTORC1" stoichiometry="1"/>

```

</listOfProducts>

<listOfModifiers>

<modifierSpeciesReference species="pAKT308"/>

<modifierSpeciesReference species="ppAKT308473"/>

</listOfModifiers>

<kineticLaw>

<math xmlns="http://www.w3.org/1998/Math/MathML">

<apply>

<minus/>

<apply>

<times/>

<apply>

<plus/>

<apply>

<times/>

<ci> kc8f1 </ci>

<ci> pAKT308 </ci>

</apply>

<apply>

<times/>

<ci> AKTscale </ci>

<ci> kc8f1 </ci>

<ci> ppAKT308473 </ci>

</apply>

</apply>

<ci> mTORC1 </ci>

</apply>

<apply>

```

    <times/>

    <ci> Vmax8r1 </ci>

    <ci> amTORC1 </ci>

  </apply>

</apply>

</math>

</kineticLaw>

</reaction>

<reaction id="R9" name="R9" reversible="true">

  <listOfReactants>

    <speciesReference species="S6K" stoichiometry="1"/>

  </listOfReactants>

  <listOfProducts>

    <speciesReference species="pS6K" stoichiometry="1"/>

  </listOfProducts>

  <listOfModifiers>

    <modifierSpeciesReference species="amTORC1"/>

  </listOfModifiers>

  <kineticLaw>

    <math xmlns="http://www.w3.org/1998/Math/MathML">

      <apply>

        <minus/>

        <apply>

          <times/>

          <ci> kc9f1 </ci>

          <ci> amTORC1 </ci>

          <ci> S6K </ci>

        </apply>

```

```

    <apply>
      <times/>
      <ci> Vmax9r1 </ci>
      <ci> pS6K </ci>
    </apply>
  </apply>
</math>
</kineticLaw>
</reaction>
<reaction id="R10" name="R10" reversible="true">
  <listOfReactants>
    <speciesReference species="FGFR" stoichiometry="1"/>
  </listOfReactants>
  <listOfProducts>
    <speciesReference species="pFGFR" stoichiometry="1"/>
  </listOfProducts>
  <listOfModifiers>
    <modifierSpeciesReference species="E2F"/>
  </listOfModifiers>
  <kineticLaw>
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply>
        <minus/>
        <apply>
          <times/>
          <ci> kc10f1 </ci>
          <ci> FGF </ci>
          <ci> FGFR </ci>

```

```

    <apply>
      <plus/>
      <cn type="integer"> 1 </cn>
    <apply>
      <times/>
      <ci> alpha10 </ci>
      <ci> E2F </ci>
    </apply>
  </apply>
</apply>
<apply>
  <times/>
  <ci> Vmax10r1 </ci>
  <ci> pFGFR </ci>
</apply>
</apply>
</math>
</kineticLaw>
</reaction>
<reaction id="R11" name="R11" reversible="true">
  <listOfReactants>
    <speciesReference species="Ras" stoichiometry="1"/>
  </listOfReactants>
  <listOfProducts>
    <speciesReference species="aRas" stoichiometry="1"/>
  </listOfProducts>
  <listOfModifiers>
    <modifierSpeciesReference species="pERK"/>

```

```

<modifierSpeciesReference species="pFGFR"/>
<modifierSpeciesReference species="pIR"/>
</listOfModifiers>
<kineticLaw>
<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply>
    <minus/>
    <apply>
      <divide/>
      <apply>
        <times/>
        <apply>
          <plus/>
          <apply>
            <times/>
            <ci> kc11f1 </ci>
            <ci> pFGFR </ci>
          </apply>
          <apply>
            <times/>
            <ci> kc11f2 </ci>
            <ci> pIR </ci>
          </apply>
        </apply>
      <ci> Ras </ci>
    </apply>
  <apply>
    <plus/>

```

```

    <cn type="integer"> 1 </cn>

    <apply>
      <divide/>
      <ci> pERK </ci>
      <ci> Ki11 </ci>
    </apply>
  </apply>
</apply>
<apply>
  <times/>
  <ci> Vmax11r1 </ci>
  <ci> aRas </ci>
</apply>
</apply>
</math>
</kineticLaw>
</reaction>
<reaction id="R12" name="R12" reversible="true">
  <listOfReactants>
    <speciesReference species="Raf" stoichiometry="1"/>
  </listOfReactants>
  <listOfProducts>
    <speciesReference species="aRaf" stoichiometry="1"/>
  </listOfProducts>
  <listOfModifiers>
    <modifierSpeciesReference species="aRas"/>
    <modifierSpeciesReference species="pAKT308"/>
    <modifierSpeciesReference species="ppAKT308473"/>
  </listOfModifiers>

```

</listOfModifiers>

<kineticLaw>

<math xmlns="http://www.w3.org/1998/Math/MathML">

<apply>

<minus/>

<apply>

<divide/>

<apply>

<times/>

<ci> kc12f1 </ci>

<ci> aRas </ci>

<ci> Raf </ci>

</apply>

<apply>

<plus/>

<cn type="integer"> 1 </cn>

<apply>

<divide/>

<ci> pAKT308 </ci>

<ci> Ki12 </ci>

</apply>

<apply>

<divide/>

<ci> ppAKT308473 </ci>

<apply>

<times/>

<ci> AKTscale </ci>

<ci> Ki12 </ci>

```

        </apply>
    </apply>
</apply>
</apply>
<apply>
    <times/>
    <ci> Vmax12r1 </ci>
    <ci> aRaf </ci>
</apply>
</apply>
</math>
</kineticLaw>
</reaction>
<reaction id="R13" name="R13" reversible="true">
    <listOfReactants>
        <speciesReference species="MEK" stoichiometry="1"/>
    </listOfReactants>
    <listOfProducts>
        <speciesReference species="pMEK" stoichiometry="1"/>
    </listOfProducts>
    <listOfModifiers>
        <modifierSpeciesReference species="aRaf"/>
    </listOfModifiers>
    <kineticLaw>
        <math xmlns="http://www.w3.org/1998/Math/MathML">
            <apply>
                <minus/>
                <apply>

```

```

    <times/>
    <ci> kc13f1 </ci>
    <ci> aRaf </ci>
    <ci> MEK </ci>
  </apply>
  <apply>
    <times/>
    <ci> Vmax13r1 </ci>
    <ci> pMEK </ci>
  </apply>
</apply>
</math>
</kineticLaw>
</reaction>
<reaction id="R14" name="R14" reversible="true">
  <listOfReactants>
    <speciesReference species="ERK" stoichiometry="1"/>
  </listOfReactants>
  <listOfProducts>
    <speciesReference species="pERK" stoichiometry="1"/>
  </listOfProducts>
  <listOfModifiers>
    <modifierSpeciesReference species="pMEK"/>
  </listOfModifiers>
  <kineticLaw>
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply>
        <minus/>

```

```

    <apply>
      <times/>
      <ci> kc14f1 </ci>
      <ci> pMEK </ci>
      <ci> ERK </ci>
    </apply>
    <apply>
      <times/>
      <ci> Vmax14r1 </ci>
      <ci> pERK </ci>
    </apply>
  </apply>
</math>
</kineticLaw>
</reaction>
<reaction id="R15" name="R15" reversible="true">
  <listOfReactants>
    <speciesReference species="ERa" stoichiometry="1"/>
  </listOfReactants>
  <listOfProducts>
    <speciesReference species="aERa" stoichiometry="1"/>
  </listOfProducts>
  <listOfModifiers>
    <modifierSpeciesReference species="FOXO3"/>
  </listOfModifiers>
  <kineticLaw>
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply>

```

$$\frac{\frac{\text{kc15f1} \times \text{Est}}{\text{ERa}} + 1}{\frac{\alpha15 \times \text{FOXO3}}{1} + 1}$$

```

    <apply>
      <times/>
      <ci> Vmax15r1 </ci>
      <ci> aERa </ci>
    </apply>
  </apply>
</math>
</kineticLaw>
</reaction>
<reaction id="R16" name="R16" reversible="false">
  <listOfProducts>
    <speciesReference species="Myc" stoichiometry="1"/>
  </listOfProducts>
  <listOfModifiers>
    <modifierSpeciesReference species="E2F"/>
    <modifierSpeciesReference species="aERa"/>
    <modifierSpeciesReference species="cycD"/>
    <modifierSpeciesReference species="pERK"/>
  </listOfModifiers>
  <kineticLaw>
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply>
        <plus/>
        <apply>
          <times/>
          <ci> kc16f1 </ci>
          <ci> aERa </ci>
        </apply>

```

```

    <plus/>
    <cn type="integer"> 1 </cn>
    <apply>
      <times/>
      <ci> alpha16a </ci>
      <ci> pERK </ci>
    </apply>
    <apply>
      <times/>
      <ci> alpha16b </ci>
      <ci> cycD </ci>
    </apply>
  </apply>
</apply>
</math>
</kineticLaw>
</reaction>
<reaction id="R17" name="R17" reversible="false">
  <listOfReactants>
    <speciesReference species="Myc" stoichiometry="1"/>
  </listOfReactants>
  <listOfModifiers>

```

```

    <modifierSpeciesReference species="GSK3b"/>
  </listOfModifiers>
  <kineticLaw>
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply>
        <times/>
        <ci> kdeg17f1 </ci>
        <ci> Myc </ci>
      <apply>
        <plus/>
        <cn type="integer"> 1 </cn>
      <apply>
        <times/>
        <ci> alpha17 </ci>
        <ci> GSK3b </ci>
      </apply>
    </apply>
  </math>
</kineticLaw>
</reaction>
<reaction id="R18" name="R18" reversible="true">
  <listOfReactants>
    <speciesReference species="Myc" stoichiometry="1"/>
  </listOfReactants>
  <listOfProducts>
    <speciesReference species="pMyc" stoichiometry="1"/>
  </listOfProducts>

```

```

<listOfModifiers>
  <modifierSpeciesReference species="pERK"/>
</listOfModifiers>
<kineticLaw>
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <minus/>
      <apply>
        <times/>
        <ci> kc18f1 </ci>
        <ci> pERK </ci>
        <ci> Myc </ci>
      </apply>
      <apply>
        <times/>
        <ci> Vmax18r1 </ci>
        <ci> pMyc </ci>
      </apply>
    </apply>
  </math>
</kineticLaw>
</reaction>
<reaction id="R19" name="R19" reversible="true">
  <listOfReactants>
    <speciesReference species="GSK3b" stoichiometry="1"/>
  </listOfReactants>
  <listOfProducts>
    <speciesReference species="pGSK3b" stoichiometry="1"/>
  </listOfProducts>
</reaction>

```

</listOfProducts>

<listOfModifiers>

<modifierSpeciesReference species="pAKT308"/>

<modifierSpeciesReference species="ppAKT308473"/>

</listOfModifiers>

<kineticLaw>

<math xmlns="http://www.w3.org/1998/Math/MathML">

<apply>

<minus/>

<apply>

<times/>

<apply>

<plus/>

<apply>

<times/>

<ci> kc19f1 </ci>

<ci> pAKT308 </ci>

</apply>

<apply>

<times/>

<ci> AKTscale </ci>

<ci> kc19f1 </ci>

<ci> ppAKT308473 </ci>

</apply>

</apply>

<ci> GSK3b </ci>

</apply>

<apply>

```

    <times/>

    <ci> Vmax19r1 </ci>

    <ci> pGSK3b </ci>

  </apply>

</apply>

</math>

</kineticLaw>

</reaction>

<reaction id="R20" name="R20" reversible="true">

  <listOfReactants>

    <speciesReference species="FOXO3" stoichiometry="1"/>

  </listOfReactants>

  <listOfProducts>

    <speciesReference species="pFOXO3" stoichiometry="1"/>

  </listOfProducts>

  <listOfModifiers>

    <modifierSpeciesReference species="pAKT308"/>

    <modifierSpeciesReference species="ppAKT308473"/>

  </listOfModifiers>

  <kineticLaw>

    <math xmlns="http://www.w3.org/1998/Math/MathML">

      <apply>

        <minus/>

        <apply>

          <times/>

          <apply>

            <plus/>

            <apply>

```

```

    <times/>
    <ci> kc20f1 </ci>
    <ci> pAKT308 </ci>
  </apply>
  <apply>
    <times/>
    <ci> AKTscale </ci>
    <ci> kc20f1 </ci>
    <ci> ppAKT308473 </ci>
  </apply>
</apply>
<ci> FOXO3 </ci>
</apply>
<apply>
  <times/>
  <ci> Vmax20r1 </ci>
  <ci> pFOXO3 </ci>
</apply>
</apply>
</math>
</kineticLaw>
</reaction>
<reaction id="R21" name="R21" reversible="false">
  <listOfProducts>
    <speciesReference species="cycD" stoichiometry="1"/>
  </listOfProducts>
  <listOfModifiers>
    <modifierSpeciesReference species="Myc"/>
  </listOfModifiers>

```

```

<modifierSpeciesReference species="aERa"/>
<modifierSpeciesReference species="amTORC1"/>
<modifierSpeciesReference species="pERK"/>
<modifierSpeciesReference species="pMyc"/>
</listOfModifiers>
<kineticLaw>
<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply>
    <plus/>
    <apply>
      <times/>
      <ci> kc21f1 </ci>
      <ci> amTORC1 </ci>
    </apply>
    <apply>
      <times/>
      <ci> kc21f2 </ci>
      <ci> pERK </ci>
    </apply>
    <apply>
      <times/>
      <ci> kc21f3 </ci>
      <apply>
        <plus/>
        <ci> Myc </ci>
        <ci> pMyc </ci>
      </apply>
    </apply>
  </apply>
</math>
</kineticLaw>

```

```

<apply>
  <times/>
  <ci> kc21f4 </ci>
  <ci> aERa </ci>
  <apply>
    <plus/>
    <cn type="integer"> 1 </cn>
    <apply>
      <times/>
      <ci> alpha21a </ci>
      <ci> pERK </ci>
    </apply>
  </apply>
  <apply>
    <times/>
    <ci> alpha21b </ci>
    <ci> cycD </ci>
  </apply>
</apply>
</math>
</kineticLaw>
</reaction>
<reaction id="R22" name="R22" reversible="false">
  <listOfReactants>
    <speciesReference species="cycD" stoichiometry="1"/>
  </listOfReactants>
  <listOfModifiers>

```

```

    <modifierSpeciesReference species="GSK3b"/>
  </listOfModifiers>
</kineticLaw>
<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply>
    <times/>
    <ci> kdeg22f1 </ci>
    <ci> cycD </ci>
    <apply>
      <plus/>
      <cn type="integer"> 1 </cn>
      <apply>
        <times/>
        <ci> alpha22 </ci>
        <ci> GSK3b </ci>
      </apply>
    </apply>
  </apply>
</math>
</reaction>
<reaction id="R23" name="R23" reversible="false">
  <listOfProducts>
    <speciesReference species="cycE" stoichiometry="1"/>
  </listOfProducts>
  <listOfModifiers>
    <modifierSpeciesReference species="E2F"/>
    <modifierSpeciesReference species="Myc"/>
  </listOfModifiers>

```

```

<modifierSpeciesReference species="pMyc"/>
</listOfModifiers>
<kineticLaw>
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <plus/>
      <apply>
        <times/>
        <ci> kc23f1 </ci>
        <ci> E2F </ci>
      <apply>
        <plus/>
        <cn type="integer"> 1 </cn>
      <apply>
        <times/>
        <ci> alpha23 </ci>
      <apply>
        <plus/>
        <ci> Myc </ci>
        <ci> pMyc </ci>
      </apply>
    </apply>
  </apply>
</kineticLaw>
</math>
</math>
<math xmlns="http://www.w3.org/1998/Math/MathML">
  <times/>
  <ci> kc23f2 </ci>
  <apply>

```

```

    <plus/>
    <ci> Myc </ci>
    <ci> pMyc </ci>
  </apply>
</apply>
</apply>
</math>
</kineticLaw>
</reaction>
<reaction id="R24" name="R24" reversible="false">
  <listOfReactants>
    <speciesReference species="cycE" stoichiometry="1"/>
  </listOfReactants>
  <listOfModifiers>
    <modifierSpeciesReference species="GSK3b"/>
  </listOfModifiers>
  <kineticLaw>
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply>
        <times/>
        <ci> kdeg24f1 </ci>
        <ci> cycE </ci>
      <apply>
        <plus/>
        <cn type="integer"> 1 </cn>
      <apply>
        <times/>
        <ci> alpha24 </ci>

```

```

      <ci> GSK3b </ci>

    </apply>

  </apply>

</apply>

</math>

</kineticLaw>

</reaction>

<reaction id="R25" name="R25" reversible="false">

  <listOfProducts>

    <speciesReference species="cycA" stoichiometry="1"/>

  </listOfProducts>

  <listOfModifiers>

    <modifierSpeciesReference species="E2F"/>

    <modifierSpeciesReference species="Myc"/>

    <modifierSpeciesReference species="pMyc"/>

  </listOfModifiers>

  <kineticLaw>

    <math xmlns="http://www.w3.org/1998/Math/MathML">

      <apply>

        <plus/>

        <apply>

          <times/>

          <ci> kc25f1 </ci>

          <ci> E2F </ci>

        </apply>

        <plus/>

        <cn type="integer"> 1 </cn>

      </apply>

```

```

    <times/>
    <ci> alpha25 </ci>
    <apply>
      <plus/>
      <ci> Myc </ci>
      <ci> pMyc </ci>
    </apply>
  </apply>
</apply>
</apply>
<apply>
  <times/>
  <ci> kc25f2 </ci>
  <apply>
    <plus/>
    <ci> Myc </ci>
    <ci> pMyc </ci>
  </apply>
</apply>
</apply>
</math>
</kineticLaw>
</reaction>
<reaction id="R26" name="R26" reversible="false">
  <listOfReactants>
    <speciesReference species="cycA" stoichiometry="1"/>
  </listOfReactants>
  <kineticLaw>

```

```

<math xmlns="http://www.w3.org/1998/Math/MathML">
  <apply>
    <times/>
    <ci> kdeg26f1 </ci>
    <ci> cycA </ci>
  </apply>
</math>
</kineticLaw>
</reaction>
<reaction id="R27" name="R27" reversible="true">
  <listOfReactants>
    <speciesReference species="cycD" stoichiometry="1"/>
    <speciesReference species="CDK46" stoichiometry="1"/>
  </listOfReactants>
  <listOfProducts>
    <speciesReference species="CDK46cycD" stoichiometry="1"/>
  </listOfProducts>
  <listOfModifiers>
    <modifierSpeciesReference species="pp2127"/>
  </listOfModifiers>
  <kineticLaw>
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply>
        <minus/>
        <apply>
          <divide/>
          <apply>
            <times/>

```

<ci> ka27f1 </ci>
 <ci> CDK46 </ci>
 <ci> cycD </ci>
 <apply>
 <plus/>
 <cn type="integer"> 1 </cn>
 <apply>
 <times/>
 <ci> alpha27 </ci>
 <ci> pp2127 </ci>
 </apply>
 </apply>
</apply>
<apply>
 <plus/>
 <cn type="integer"> 1 </cn>
<apply>
 <divide/>
 <ci> CDK46i_0 </ci>
 <ci> Ki27 </ci>
</apply>
</apply>
</apply>
<apply>
 <times/>
 <ci> kd27r1 </ci>
 <ci> CDK46cycD </ci>
</apply>

```

    </apply>
  </math>
</kineticLaw>
</reaction>
<reaction id="R28" name="R28" reversible="true">
  <listOfReactants>
    <speciesReference species="cycE" stoichiometry="1"/>
    <speciesReference species="CDK2" stoichiometry="1"/>
  </listOfReactants>
  <listOfProducts>
    <speciesReference species="CDK2cycE" stoichiometry="1"/>
  </listOfProducts>
  <listOfModifiers>
    <modifierSpeciesReference species="p2127"/>
  </listOfModifiers>
  <kineticLaw>
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply>
        <minus/>
        <apply>
          <divide/>
          <apply>
            <times/>
            <ci> ka28f1 </ci>
            <ci> CDK2 </ci>
            <ci> cycE </ci>
          </apply>
        </apply>
      </math>
    </kineticLaw>
  </reaction>

```

```

    <plus/>
    <cn type="integer"> 1 </cn>
    <apply>
      <divide/>
      <ci> p2127 </ci>
      <ci> Ki28 </ci>
    </apply>
  </apply>
</apply>
<apply>
  <times/>
  <ci> kd28r1 </ci>
  <ci> CDK2cycE </ci>
</apply>
</apply>
</math>
</kineticLaw>
</reaction>
<reaction id="R29" name="R29" reversible="true">
  <listOfReactants>
    <speciesReference species="cycA" stoichiometry="1"/>
    <speciesReference species="CDK2" stoichiometry="1"/>
  </listOfReactants>
  <listOfProducts>
    <speciesReference species="CDK2cycA" stoichiometry="1"/>
  </listOfProducts>
  <listOfModifiers>
    <modifierSpeciesReference species="pAKT308"/>

```

```

<modifierSpeciesReference species="ppAKT308473"/>
</listOfModifiers>
<kineticLaw>
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <minus/>
      <apply>
        <times/>
        <ci> ka29f1 </ci>
        <ci> CDK2 </ci>
        <ci> cycA </ci>
      <apply>
        <plus/>
        <cn type="integer"> 1 </cn>
      <apply>
        <times/>
        <ci> alpha29 </ci>
        <ci> pAKT308 </ci>
      </apply>
      <apply>
        <times/>
        <ci> AKTscale </ci>
        <ci> alpha29 </ci>
        <ci> ppAKT308473 </ci>
      </apply>
    </apply>
  </math>
</kineticLaw>

```

```

    <times/>

    <ci> kd29r1 </ci>

    <ci> CDK2cycA </ci>

  </apply>

</apply>

</math>

</kineticLaw>

</reaction>

<reaction id="R30" name="R30" reversible="true">

  <listOfReactants>

    <speciesReference species="p2127" stoichiometry="1"/>

  </listOfReactants>

  <listOfProducts>

    <speciesReference species="pp2127" stoichiometry="1"/>

  </listOfProducts>

  <listOfModifiers>

    <modifierSpeciesReference species="Myc"/>

    <modifierSpeciesReference species="pAKT308"/>

    <modifierSpeciesReference species="pMyc"/>

    <modifierSpeciesReference species="ppAKT308473"/>

  </listOfModifiers>

  <kineticLaw>

    <math xmlns="http://www.w3.org/1998/Math/MathML">

      <apply>

        <minus/>

        <apply>

          <times/>

          <apply>

```

<plus/>
<apply>
 <times/>
 <ci> kc30f1 </ci>
 <ci> pAKT308 </ci>
</apply>
<apply>
 <times/>
 <ci> AKTscale </ci>
 <ci> kc30f1 </ci>
 <ci> ppAKT308473 </ci>
</apply>
</apply>
<ci> p2127 </ci>
<apply>
 <plus/>
 <cn type="integer"> 1 </cn>
<apply>
 <times/>
 <ci> alpha30 </ci>
 <apply>
 <plus/>
 <ci> Myc </ci>
 <ci> pMyc </ci>
 </apply>
</apply>
</apply>
</apply>

```

    <apply>
      <times/>
      <ci> Vmax30r1 </ci>
      <ci> pp2127 </ci>
    </apply>
  </apply>
</math>
</kineticLaw>
</reaction>
<reaction id="R31" name="R31" reversible="false">
  <listOfProducts>
    <speciesReference species="E2F" stoichiometry="1"/>
  </listOfProducts>
  <listOfModifiers>
    <modifierSpeciesReference species="Myc"/>
    <modifierSpeciesReference species="pMyc"/>
  </listOfModifiers>
  <kineticLaw>
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply>
        <plus/>
        <apply>
          <times/>
          <ci> kc31f1 </ci>
        </apply>
        <plus/>
        <ci> Myc </ci>
        <ci> pMyc </ci>
      </apply>
    </math>
  </kineticLaw>
</reaction>

```

```

    </apply>
  </apply>
  <apply>
    <times/>
    <ci> kc31f2 </ci>
    <ci> E2F </ci>
  </apply>
</apply>
</math>
</kineticLaw>
</reaction>
<reaction id="R32" name="R32" reversible="false">
  <listOfReactants>
    <speciesReference species="E2F" stoichiometry="1"/>
  </listOfReactants>
  <kineticLaw>
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply>
        <times/>
        <ci> kdeg32f1 </ci>
        <ci> E2F </ci>
      </apply>
    </math>
  </kineticLaw>
</reaction>
<reaction id="R33" name="R33" reversible="true">
  <listOfReactants>
    <speciesReference species="E2F" stoichiometry="1"/>

```

```

    <speciesReference species="Rb" stoichiometry="1"/>
  </listOfReactants>
  <listOfProducts>
    <speciesReference species="RbE2F" stoichiometry="1"/>
  </listOfProducts>
  <kineticLaw>
    <math xmlns="http://www.w3.org/1998/Math/MathML">
      <apply>
        <minus/>
        <apply>
          <times/>
          <ci> ka33f1 </ci>
          <ci> E2F </ci>
          <ci> Rb </ci>
        </apply>
        <apply>
          <times/>
          <ci> kd33r1 </ci>
          <ci> RbE2F </ci>
        </apply>
      </apply>
    </math>
  </kineticLaw>
</reaction>
<reaction id="R34" name="R34" reversible="true">
  <listOfReactants>
    <speciesReference species="Rb" stoichiometry="1"/>
  </listOfReactants>

```

```

<listOfProducts>

  <speciesReference species="pRb" stoichiometry="1"/>

</listOfProducts>

<listOfModifiers>

  <modifierSpeciesReference species="CDK46cycD"/>

</listOfModifiers>

<kineticLaw>

  <math xmlns="http://www.w3.org/1998/Math/MathML">

    <apply>

      <minus/>

      <apply>

        <times/>

        <ci> kc34f1 </ci>

        <ci> CDK46cycD </ci>

        <ci> Rb </ci>

      </apply>

      <apply>

        <times/>

        <ci> Vmax34r1 </ci>

        <ci> pRb </ci>

      </apply>

    </apply>

  </math>

</kineticLaw>

</reaction>

<reaction id="R35" name="R35" reversible="true">

  <listOfReactants>

    <speciesReference species="pRb" stoichiometry="1"/>

```

```

</listOfReactants>

<listOfProducts>
  <speciesReference species="pppRb" stoichiometry="1"/>
</listOfProducts>

<listOfModifiers>
  <modifierSpeciesReference species="CDK2cycE"/>
</listOfModifiers>

<kineticLaw>
  <math xmlns="http://www.w3.org/1998/Math/MathML">
    <apply>
      <minus/>
      <apply>
        <times/>
        <ci> kc35f1 </ci>
        <ci> CDK2cycE </ci>
        <ci> pRb </ci>
      </apply>
      <apply>
        <times/>
        <ci> Vmax35r1 </ci>
        <ci> pppRb </ci>
      </apply>
    </apply>
  </math>
</kineticLaw>
</reaction>
</listOfReactions>
</model>

```

</sbml>