

1<sup>st</sup> grade: Ligand-receptor interaction in EGFR

**Summary:** EGF receptor (EGFR/ErbB1R) is expressed on many types of cells including epithelial and neuronal cells. EGFR is a receptor tyrosine kinase, and is activated by the binding of EGF resulting in the activation of MAPK pathway. EGFR forms dimer by the binding of EGF resulting in the stabilization of EGFR, and hence intermolecular phosphorylation within a dimer proceeds leading to the signal transduction to downstream proteins (Fig.1).

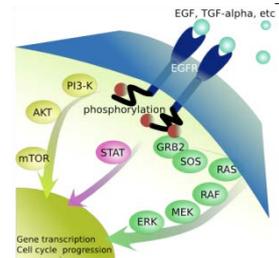
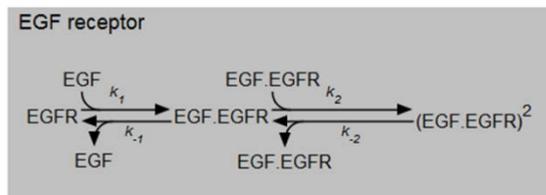


Fig.1 Signal transduction of EGFR

**Cartoon and A-Cell model:** There have published many research papers on EGFR. Schoeberl reported simulation study in detail on the pathway beginning at EGFR and ending at MAPK. Here we extract a part of EGFR activation from their study for its modeling by A-Cell. Cartoon is shown in the upper panel in Fig.2. The binding between EGF and EGFR and the dimer formation of the complex are described. The bound EGF is dissociated from EGF:EGFR complex, which is shown by bi-directional arrows. A-Cell model is shown in the middle panel. The structure of the reaction is clearly shown in the model.  $(EGF:EGFR)^2$  is a dimer.



Simulation result is shown in the bottom panel, where EGF was applied continuously at a constant concentration. To realize this, select “const” radio button in the symbol property window. Simulation

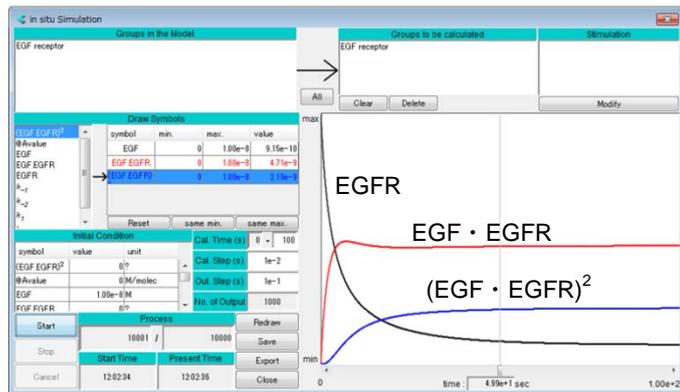


Fig.2 Cartoon for EGFR activation (top), A-Cell model (middle), and simulation result (bottom).

condition was as follows: simulation time = 0-100 s; calculation step = 10 ms; output step = 0.1 s. In this simulation, dimer  $(EGF:EGFR)^2$  reached equilibrium around t=100 s. Therefore, dose-response curve can be drawn by plotting equilibrium concentrations of  $(EGF:EGFR)^2$  by different EGF concentrations. It will be interesting to draw the curve.

**References:** Schoeberl, B., et al., Nat.Biotech., 2002, 370.  
 Hornberg, J.J., et al., Oncogene, 2005, 5533.  
 Klein, P., et al., PNAS, 2004, 929.