Rule-Based Modeling with Cellucidate

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What is Cellucidate?

Cellucidate is a web-based platform for:

- storing and organizing mechanistic biological knowledge in a biologically realistic idiom (**reaction rules**)
- evaluating this knowledge using various static and dynamic methods – a.k.a., simulation
- sharing this knowledge with others
- building upon the knowledge of others

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Mechanistic Biological Knowledge

The phosphotyrosine interaction domain of Shc binds an LXNPXY motif on the epidermal growth factor receptor.

Batzer AG, **Blaikie P**, **Nelson K**, **Schlessinger J**, **Margolis B**.

Department of Pharmacology, New York University Medical Center, New York, USA.

Shc is an SH2 domain protein that is tyrosine phosphorylated in cells stimulated with a variety of growth factors and cytokines. Once phosphorylated, Shc binds the Grb2-Sos complex, leading to Ras activation. Shc can interact with tyrosine-phosphorylated proteins by binding to phosphotyrosine in the context of an NPXpY motif, where pY is a phosphotyrosine. This is an unusual binding site for an SH2 domain protein whose binding specificity is usually controlled by residues carboxy terminal, not amino terminal, to the phosphotyrosine. Recently we identified a second region in Shc, named the phosphotyrosine interaction (PI) domain, and we have found it to be present in a variety of other cellular proteins. In this study we used a dephosphorylation protection assay, competition analysis with phosphotyrosine-containing synthetic peptides, and epidermal growth factor receptor (EGFR) mutants to determine the binding sites of the PI domain of Shc on the EGFR. We demonstrate that the PI domain of Shc binds the LXNPXpY motif that encompasses Y-1148 of the activated EGFR. We conclude that the PI domain imparts to Shc its ability to bind the NPXpY motif.

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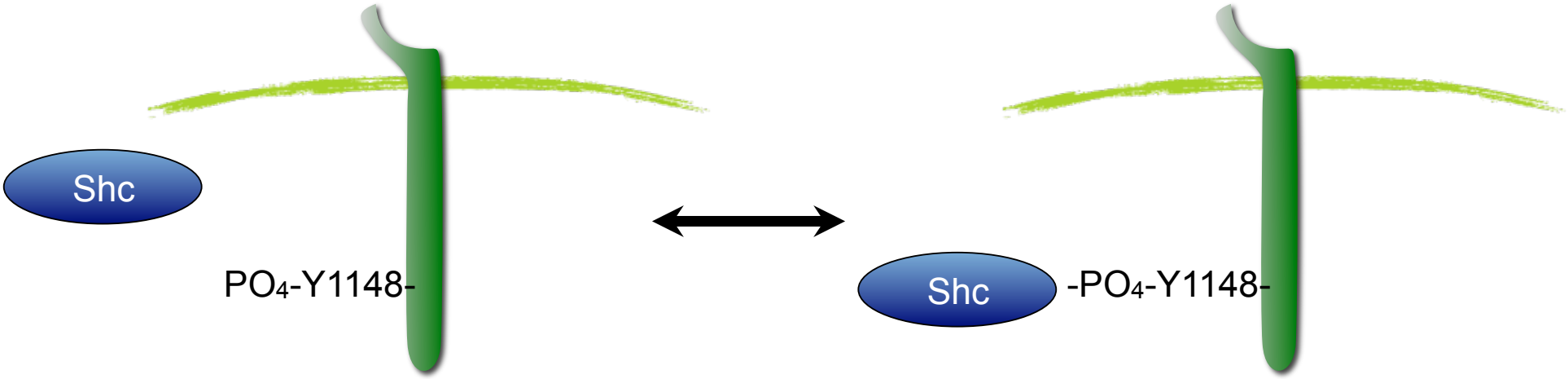
Storing Mechanistic Biological Knowledge



SBML:

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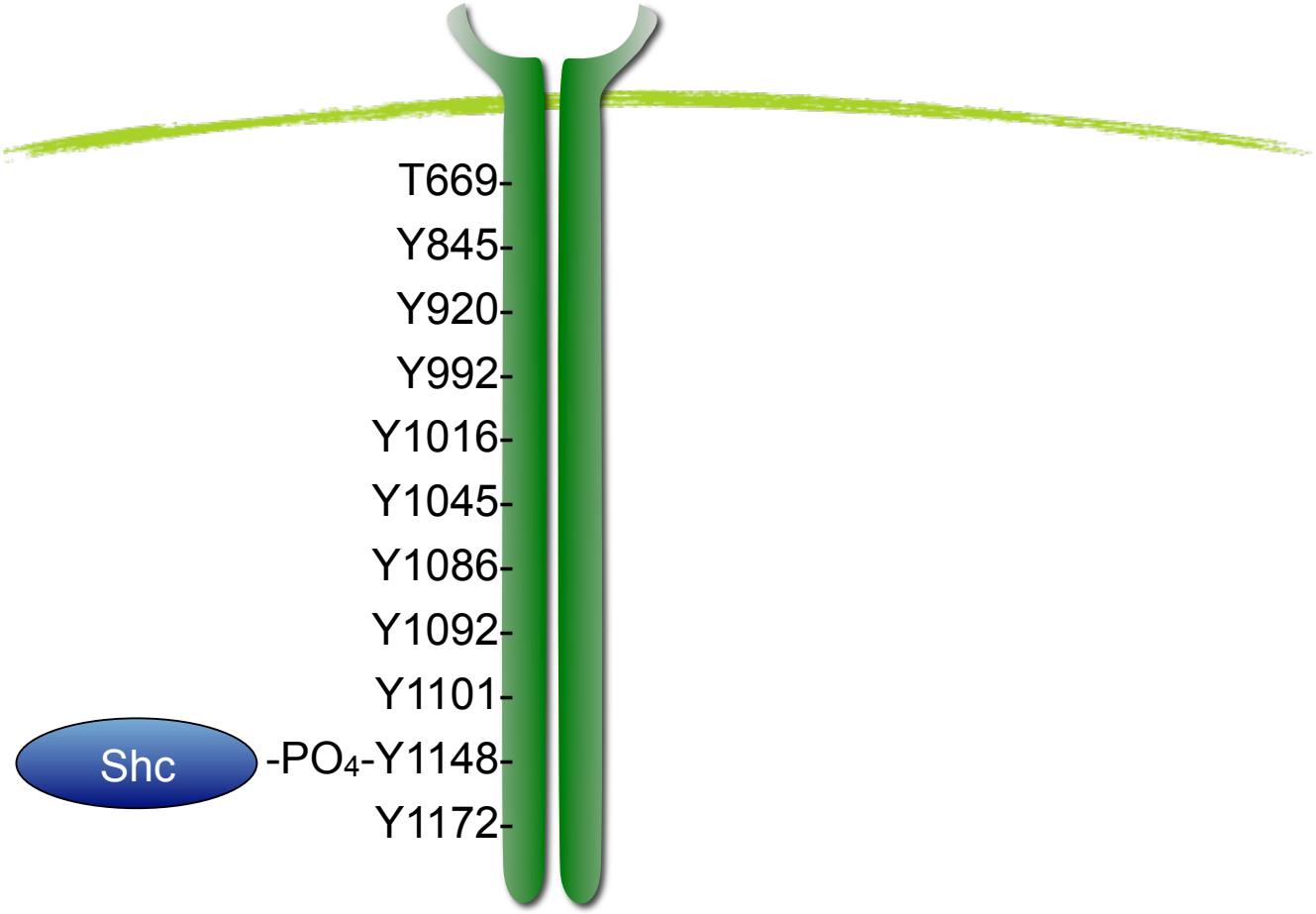
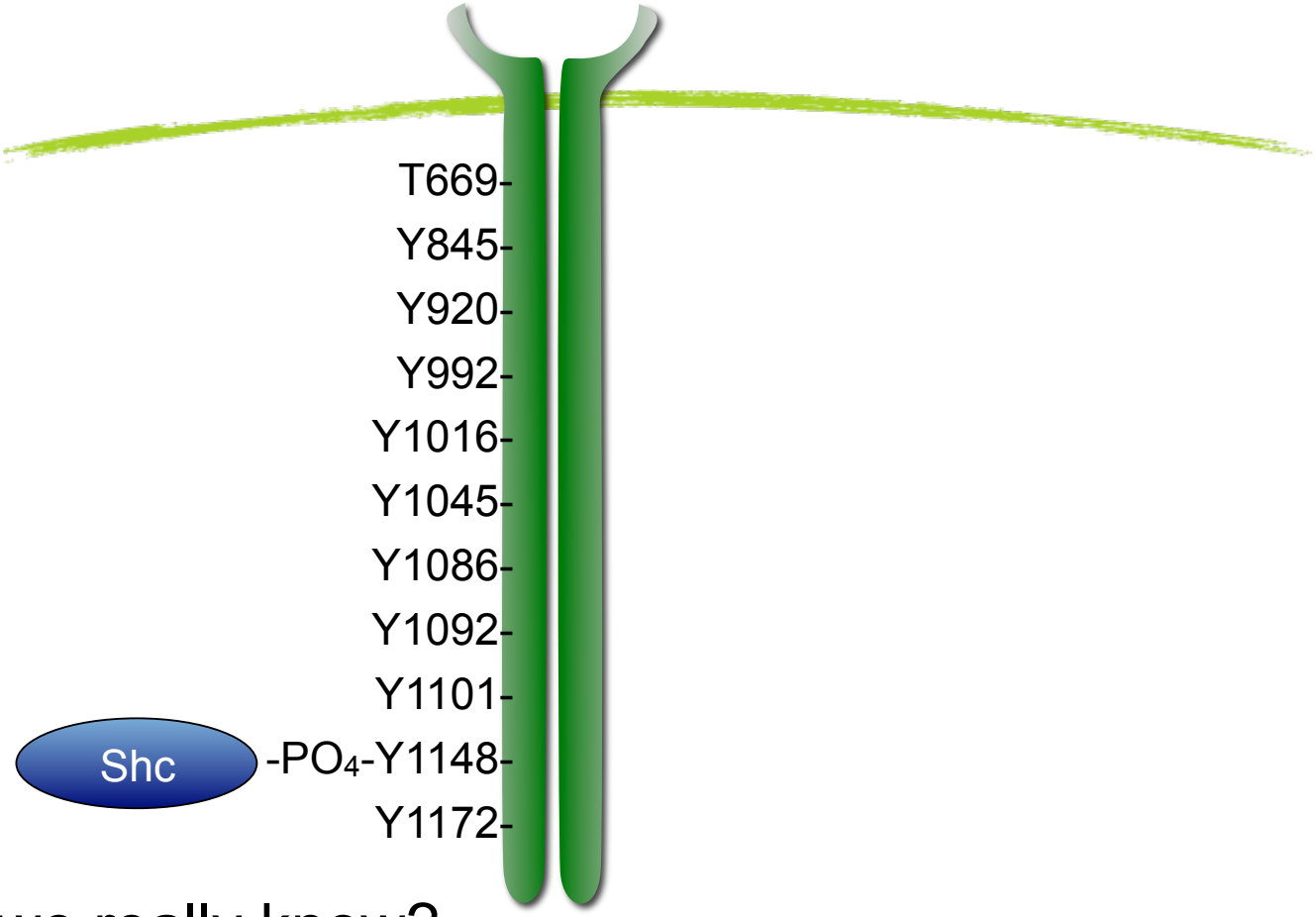
What About Additional Complexity?

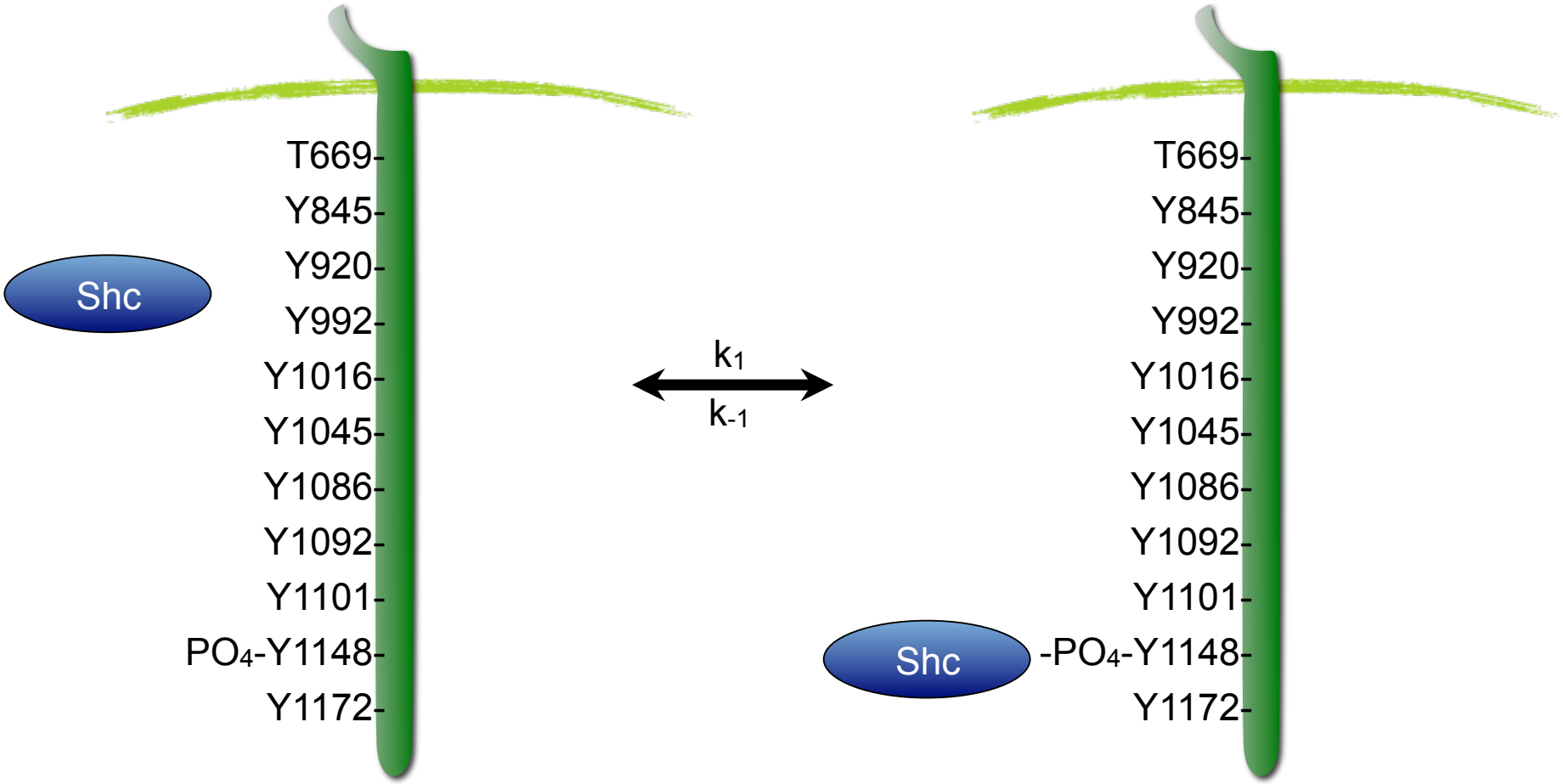


What About Additional Complexity?

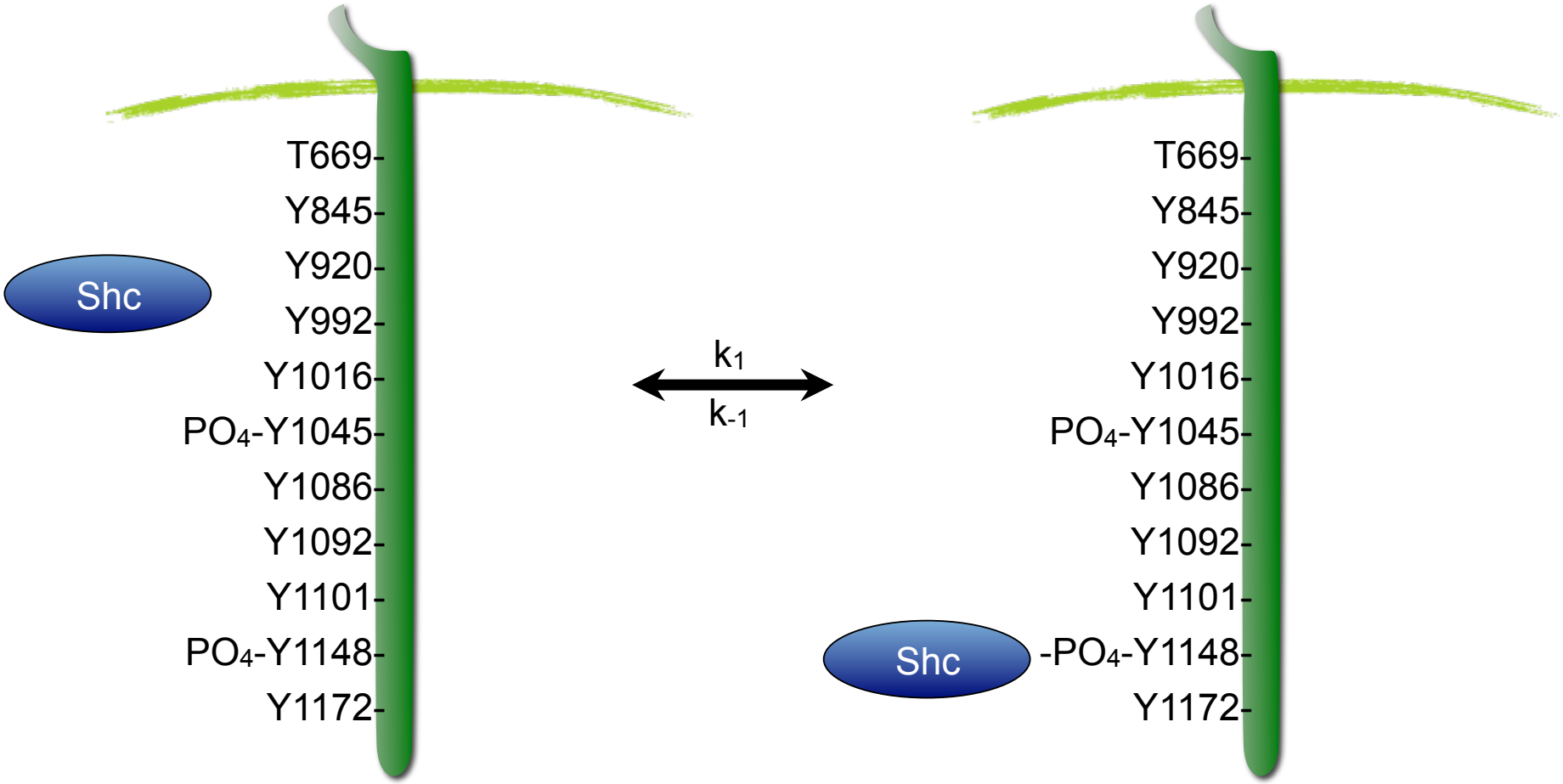


- What do we really know?
  - Assume that other sites on EGFR (and Shc) don't affect binding between EGFR and Shc

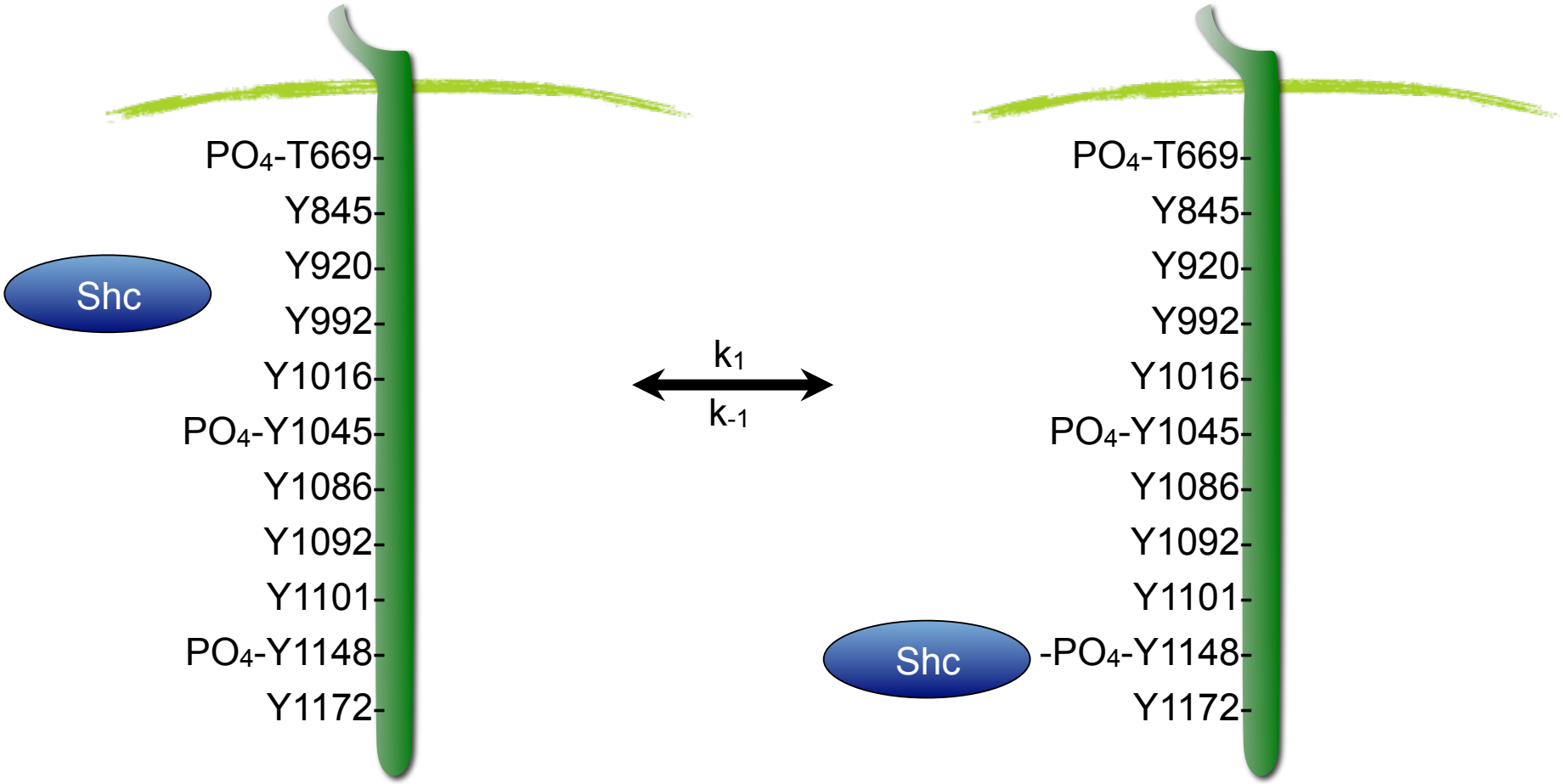
Shc Binding to EGFR - Case 1



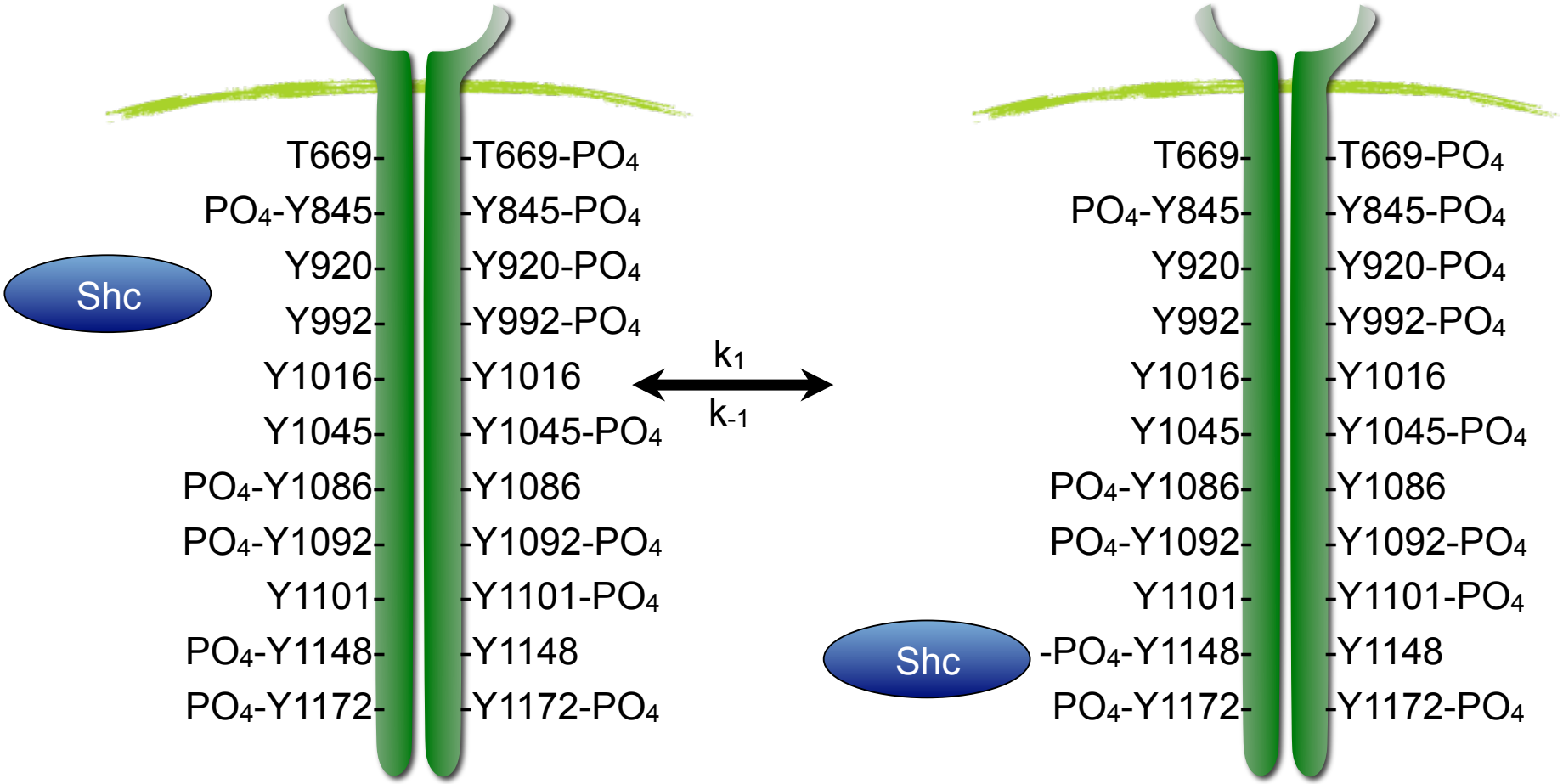
Shc Binding to EGFR - Case 2



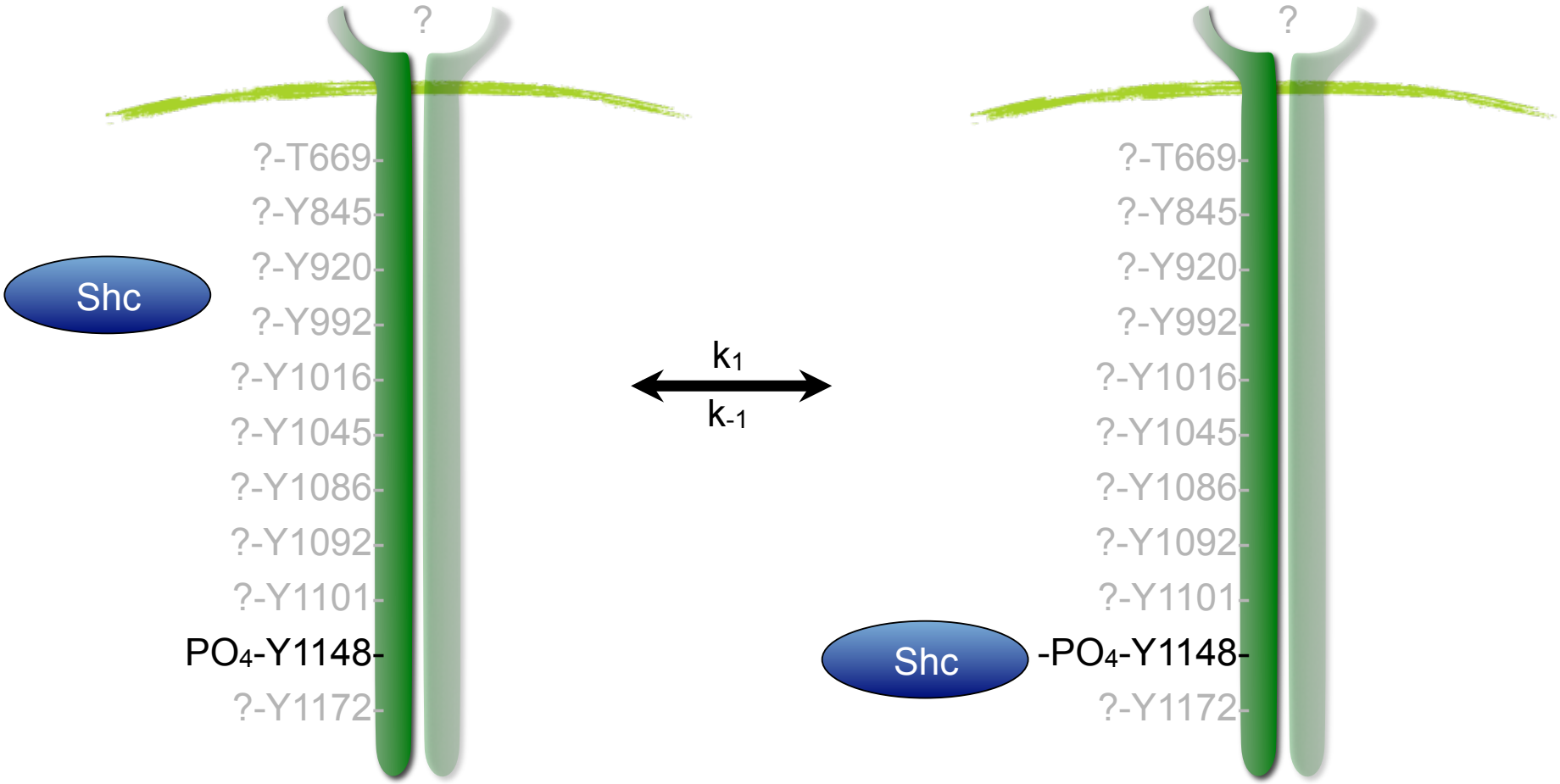
Shc Binding to EGFR - Case 3



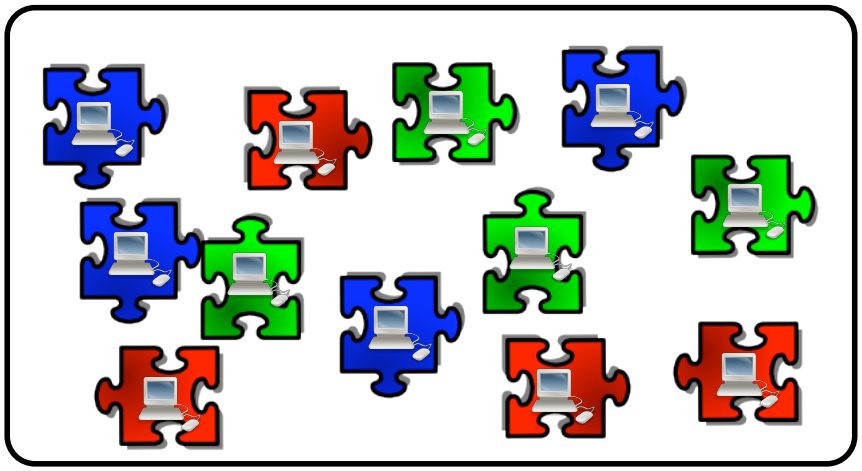
Shc Binding to EGFR - Case 1,003,442

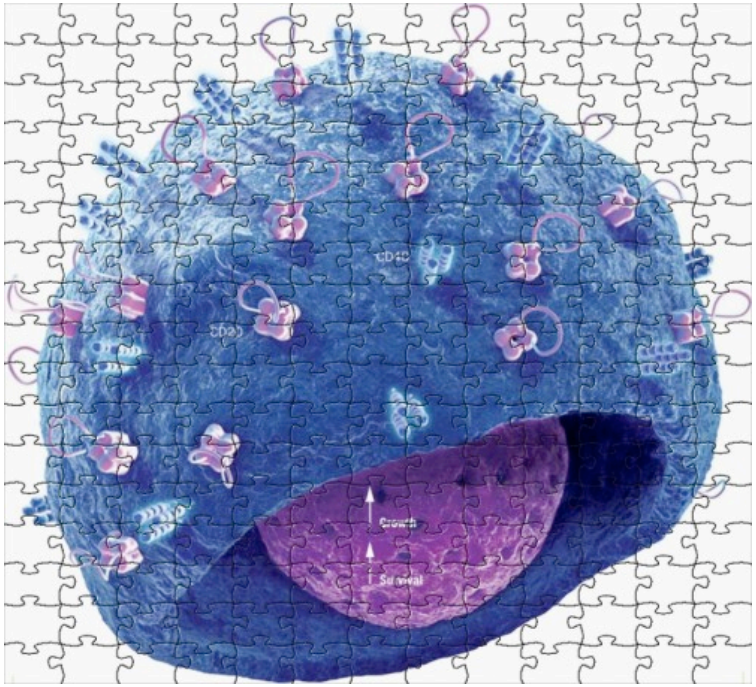


A More General Description - Reaction Rules



From Rules to a Model





Features of Reaction Rules

- Rules are correspond to the granularity of our understanding
- Rule are modular
  - Easy to update a model by changing assumption
  - Easy to combine/merge multiple models

Features of Cellucidate

- Model building
  - Intuitive graphical interface for building model
- Simulation
  - Stochastic (SSA) and ODE-based simulators that scale weakly or not at all with possible number of complexes
- Collaboration
  - Multiple users can edit same model
- Publishing
  - Models can be made available for viewing or use by wider scientific community

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How Do I Access Cellucidate?

Cellucidate is in Beta

http://www.cellucidate.com

ty@plectix.com

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