

---

Lecture 4. Protein kinases are activated and inhibited by binding partners. How does this work? We look at the structure of a well regulated three-protein complex. This paper is the first report of profound structural changes on forming a protein assembly. It is important because it shows how protein interfaces can reform and how protein segments can mimic small molecule metabolites.

**Russo AA; Jeffrey PD; Patten AK; Massague J; Pavletich NP. Crystal structure of the p27Kip1 cyclin-dependent-kinase inhibitor bound to the cyclin A-Cdk2 complex. Nature, 1996 Jul 25, 382(6589):325-31.**

What the paper is about-

- Multiple interactions to build a three protein complex
- Protein mimic of ATP, a small molecule
- Large-scale interactions and changes in protein structure on complex formation

---

### **Gibbs**

Summarize the previous papers on CDK structural work and how these relate to the function of the enzyme.

### **Sanger**

How much of KIP is necessary to inhibit cyclin-CDK2?

What three strategies are used to inhibit CDK-2?

What is the structure of p27 when not bound?

What is the buried surface relationship to Kdis?

### **Pauling**

What is the role of LFG motif? What does G do?

How does the amphipathic helix interact?

What does the C-terminal beta strand do to CDK2 N terminal domain?

What is the best indicator of important contacts?

### **Franklin**

What does p27 85-90 helix do?

What is the argument for LFG cyclin being the initial anchor?

---

Summarize what we have learned about protein interfaces in regulation of this protein kinase.