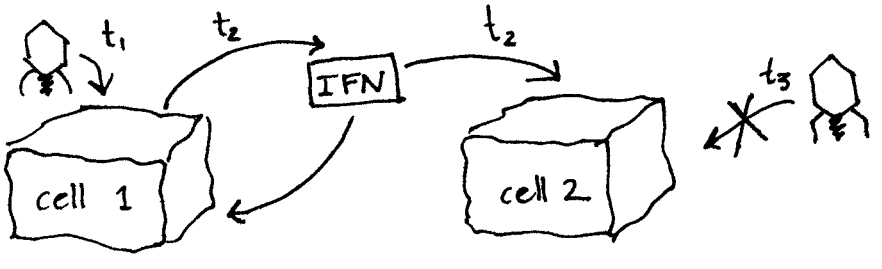
BE. 440
13 October 2004
Essigmann

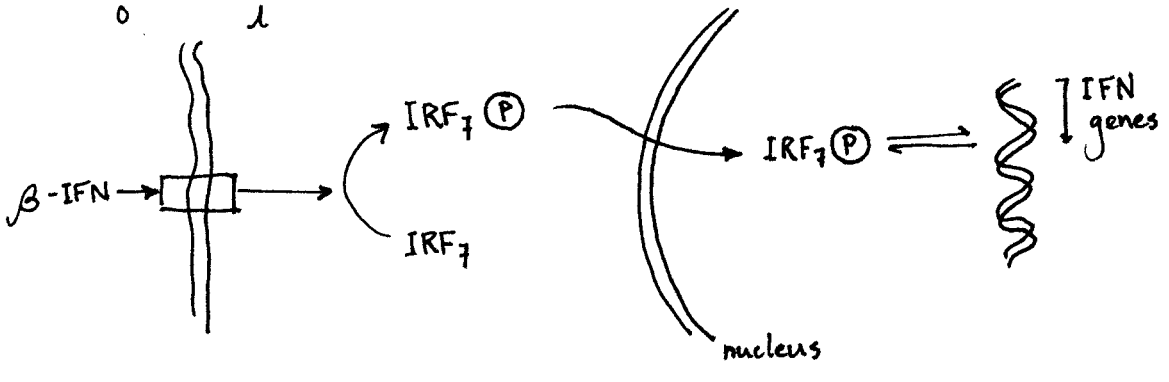
Topic: IFN induction of antiviral response

Last Day: Viral induction of IFN network
Today: IFN Induction of antiviral response
how virus invader is killed

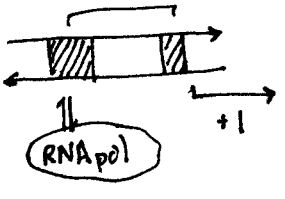
LTF: transcription factor out in cytoplasm, gets a signal and goes into nucleus and works with other TFs.
ex| IRF_3

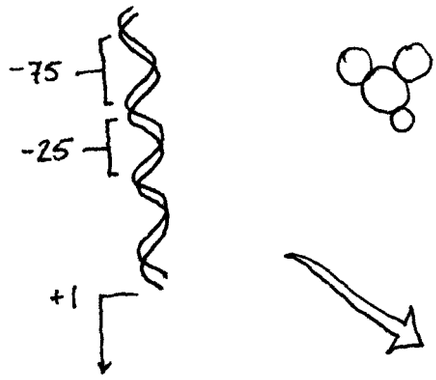
First → A bit more on IFN production and maturation





Transcription Complex:

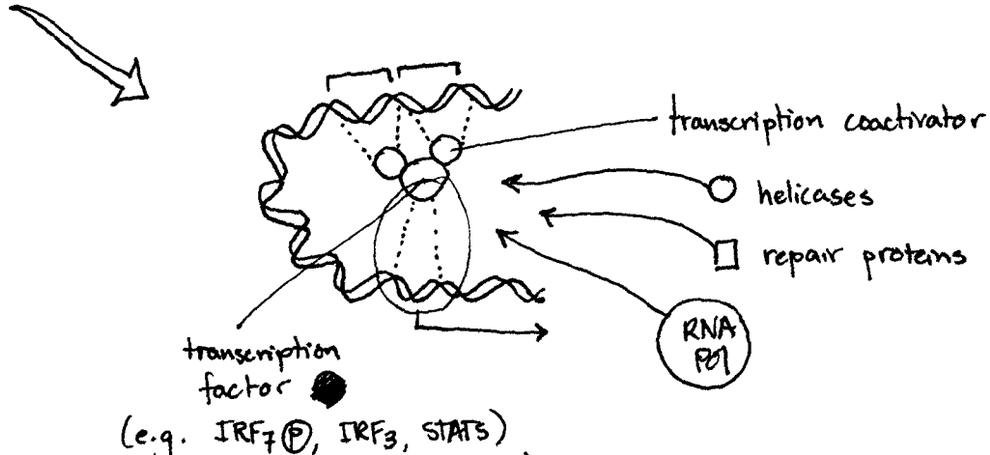




IRF_7 (P)

RNA Pol

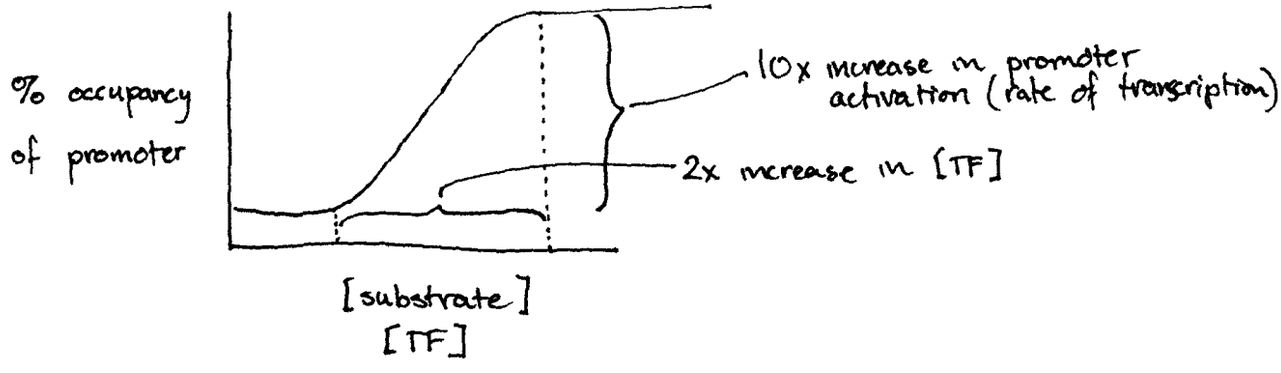
⇨ How do they find their regions? Bend DNA 180°...



(e.g. IRF_7 (P), IRF_3, STATs)

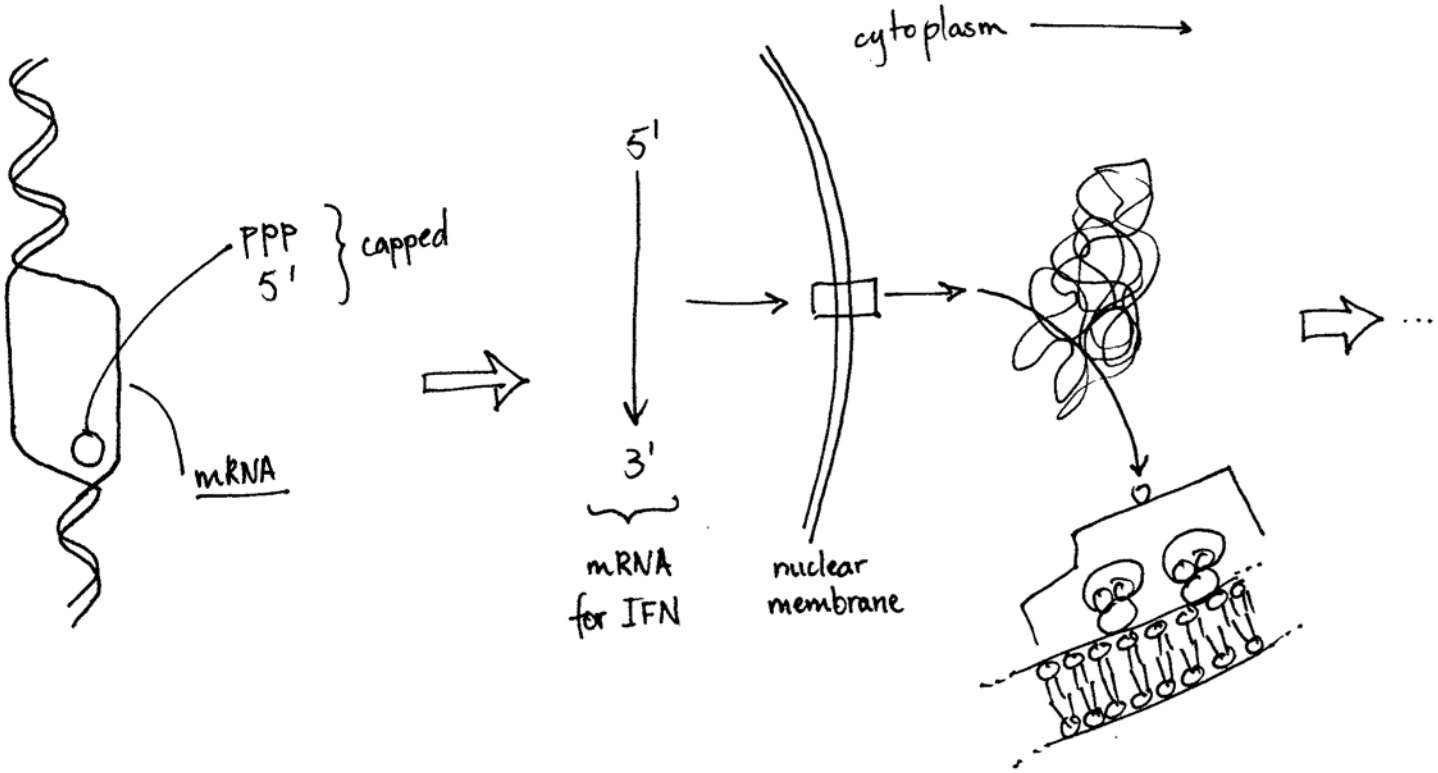
⇨ Creates a permissive environment for RNA polymerase to work. Also other players in this complex

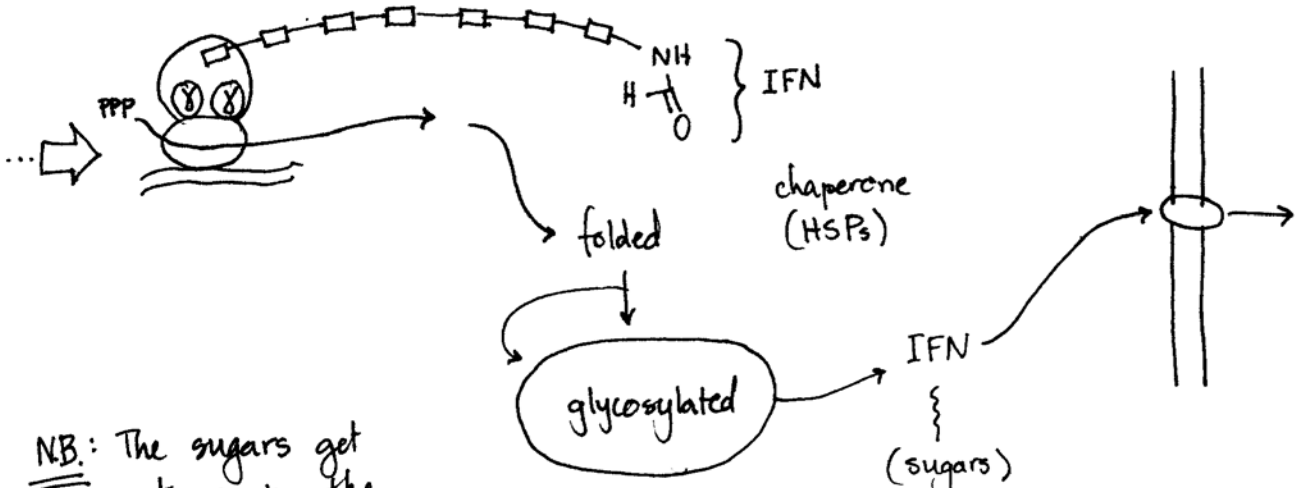
⇨ TFs are always acting together, never as monomers (always dimers, trimers) → because of cooperativity. Nature uses cooperativity to allow you to do switching. It's one way networks get switched on & off. The dimers are regulatory steps in the pathway where you can stop the flow: they're switches.



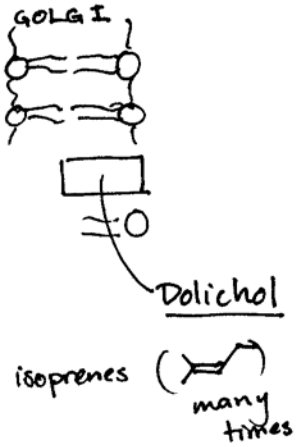
⇨ A small increase in TF leads to a disproportionately large increase in the rate of transcription

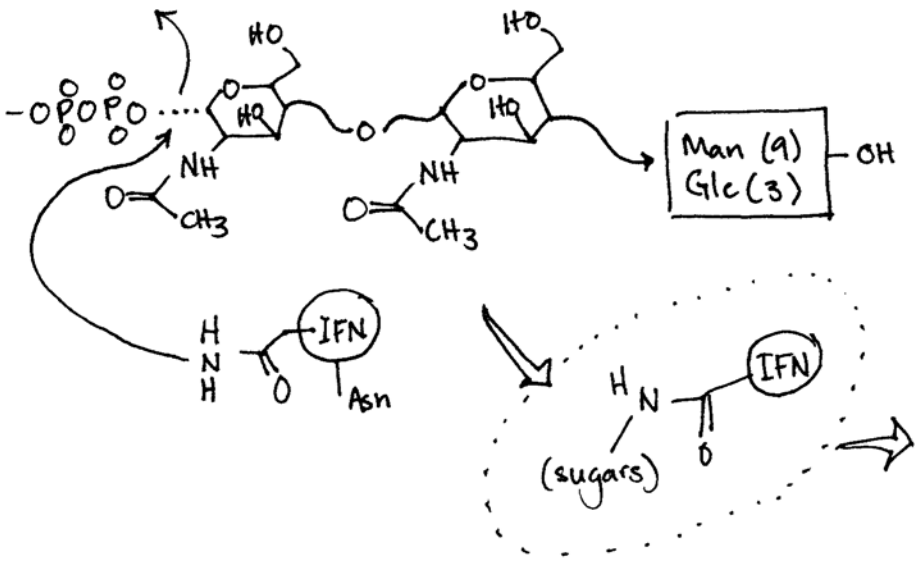
nH = measure of cooperativity (Hill constant)

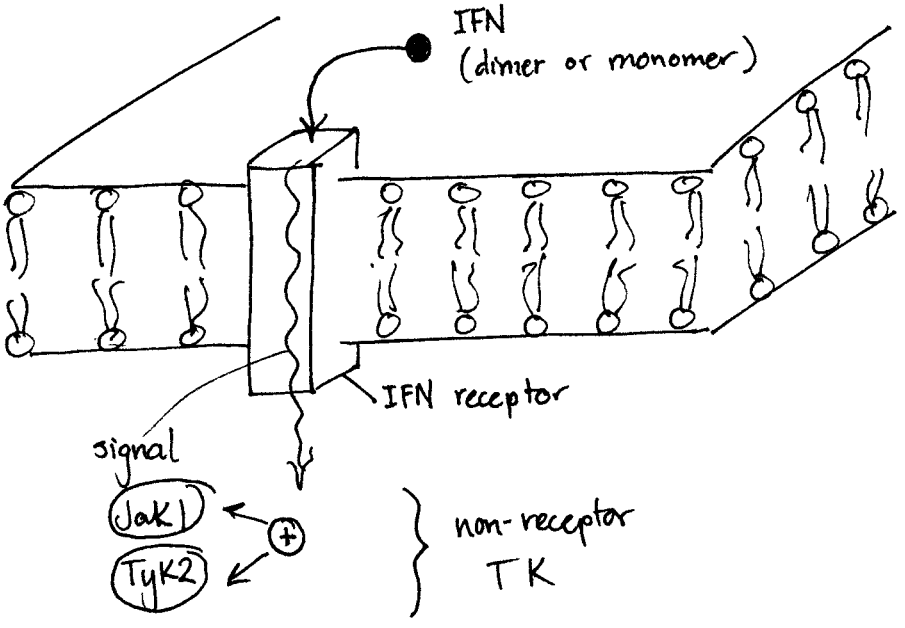




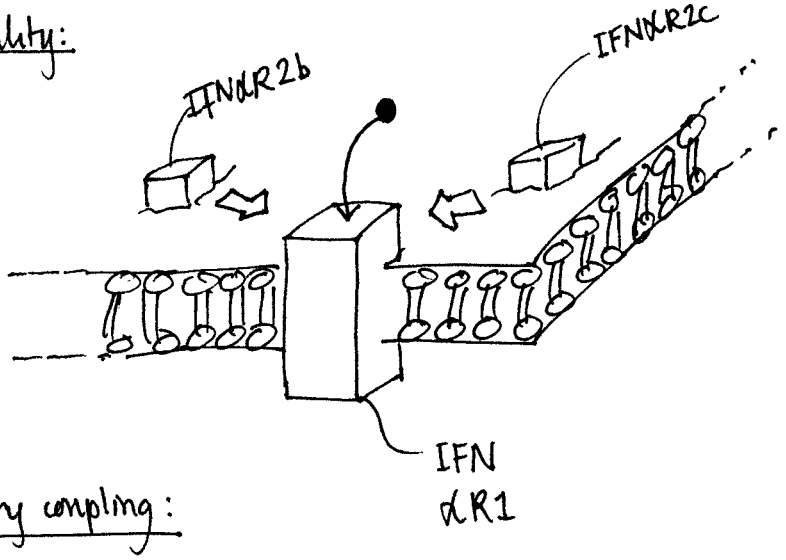
N.B.: The sugars get put on in the Endoplasmic Reticulum; then it goes to the golgi ...







More like reality:

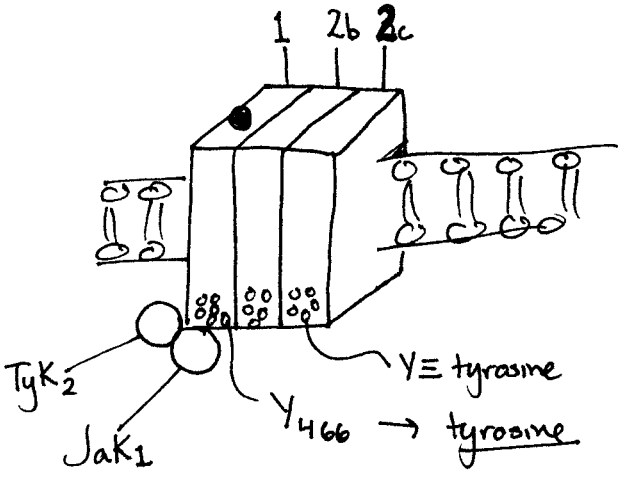


① ligand interaction

② receptor clustering

⇨ ternary coupling:

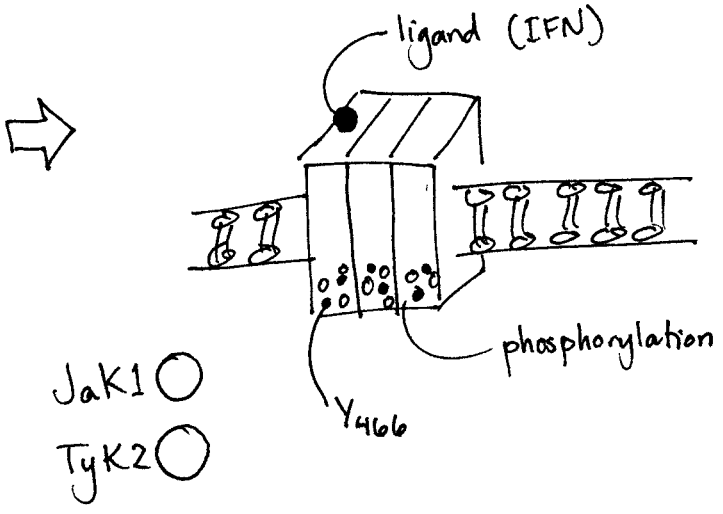
forming a complete receptor by bringing together 3 parts



③ JaK1, TyK2 recruited to receptor complex

④ JaK1, Tyk2 phosphorylate themselves, which activates them to be able to do other things

⇨

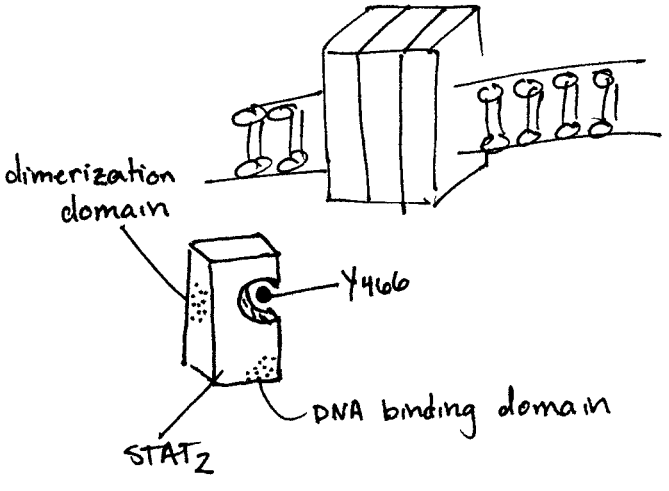


⑤ Jak & TyK phosphorylate Y_{466} on IFNαR1

⑥ Y_{466} - Ⓟ attracts STAT2

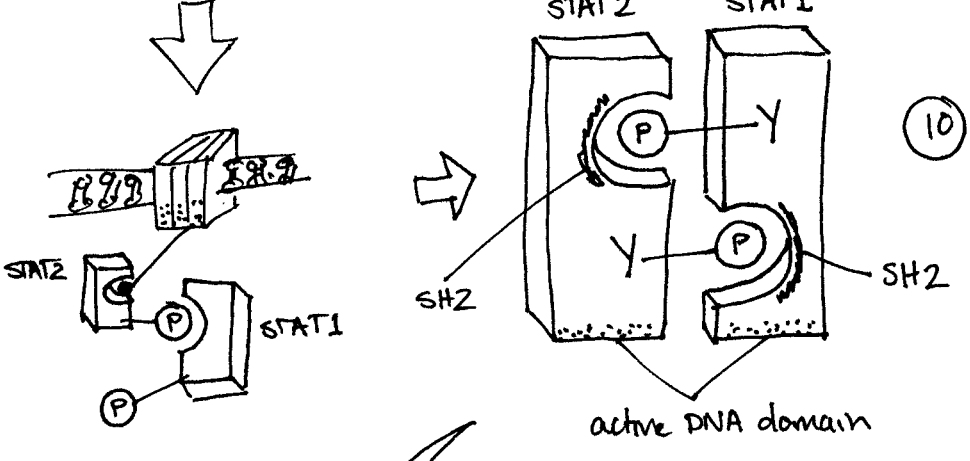
⑦ JaK/TyK phosphorylate Y_{OH} on STAT2

⑧ Y - Ⓟ on STAT2 attracts STAT 1 ↓ Y_{OH}

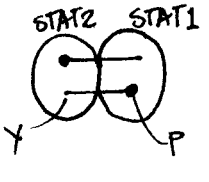


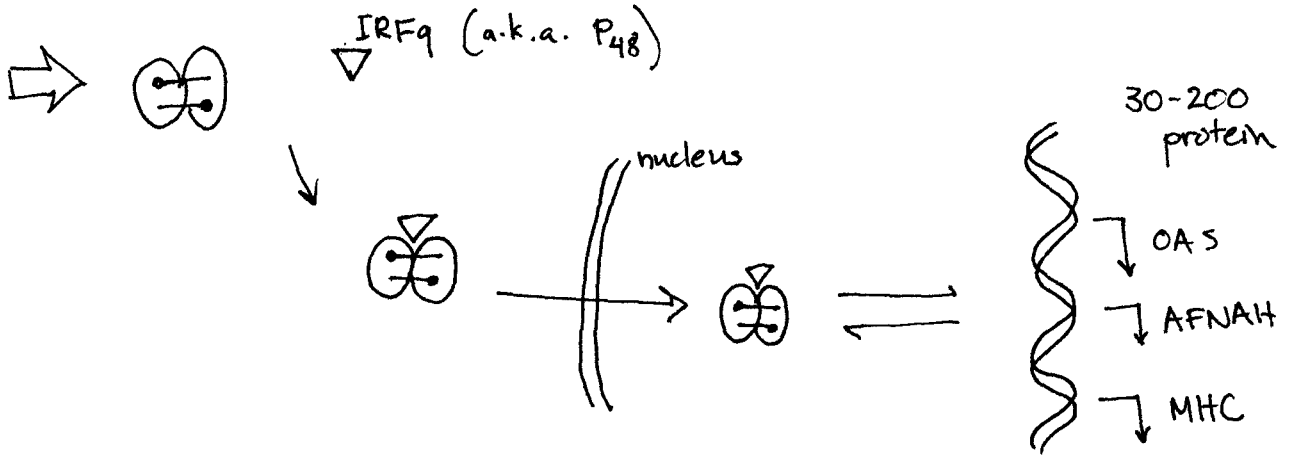
⑨ Release of STAT2/STAT1 complex

⑩ Restructuring into "TF" conformation



SHORTHAND:



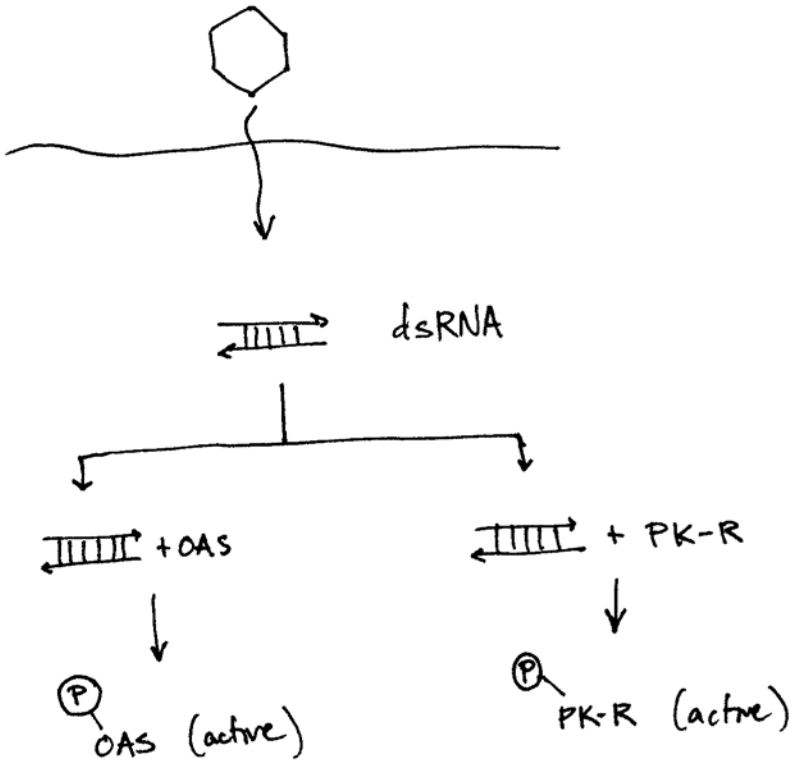


JaKs	STATs	IRFs
JaK1	STAT 1	↓
JaK2	2	10 of them
JaK3	3	
TyK2	4	
	5a	
	5b	
	6	

⇨ How does this actually result in cells becoming refractory to viruses? Next...

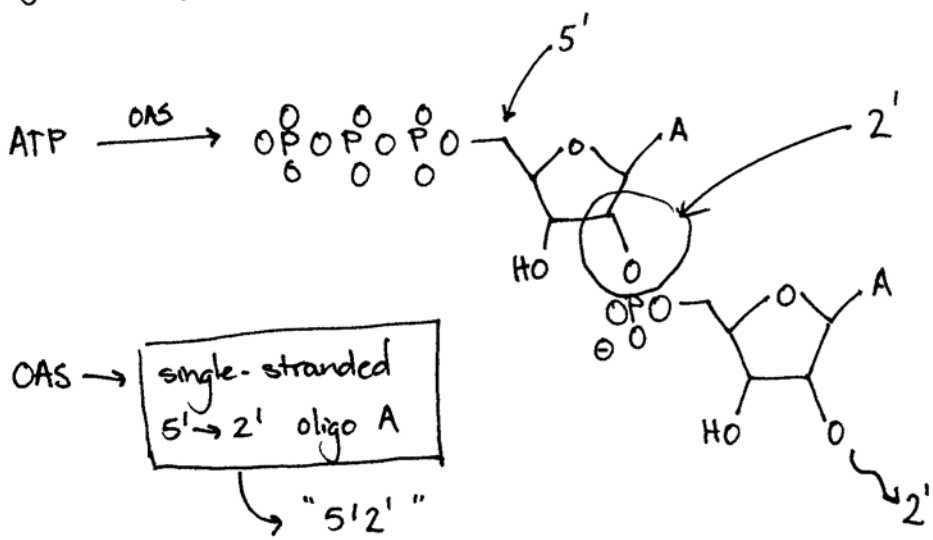
⇨ Not all STATs involve the induction of responses: some cause the suppression of responses. Need a quick switch-off sometimes. Viruses (see reading) have developed decay molecules, things that take off the phosphates, etc.

⇨ We're now in cell 2 at t_3:



⇨ Oligo (A) Synthetase:

5' → 2'



OAS → single-stranded 5' → 2' oligo A

"5'2'"

RNase L (inactive) → RNase L (active) → digests dsRNA genome of virus

⇨ Ribosomal Inactivation with PK-R: