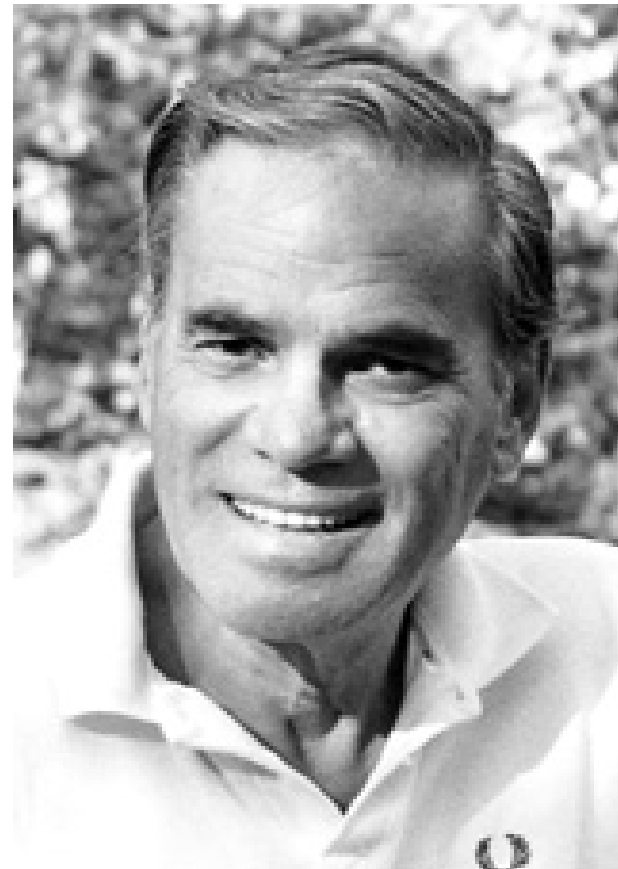


**Structure,  
function and mechanisms  
of G-Proteins**

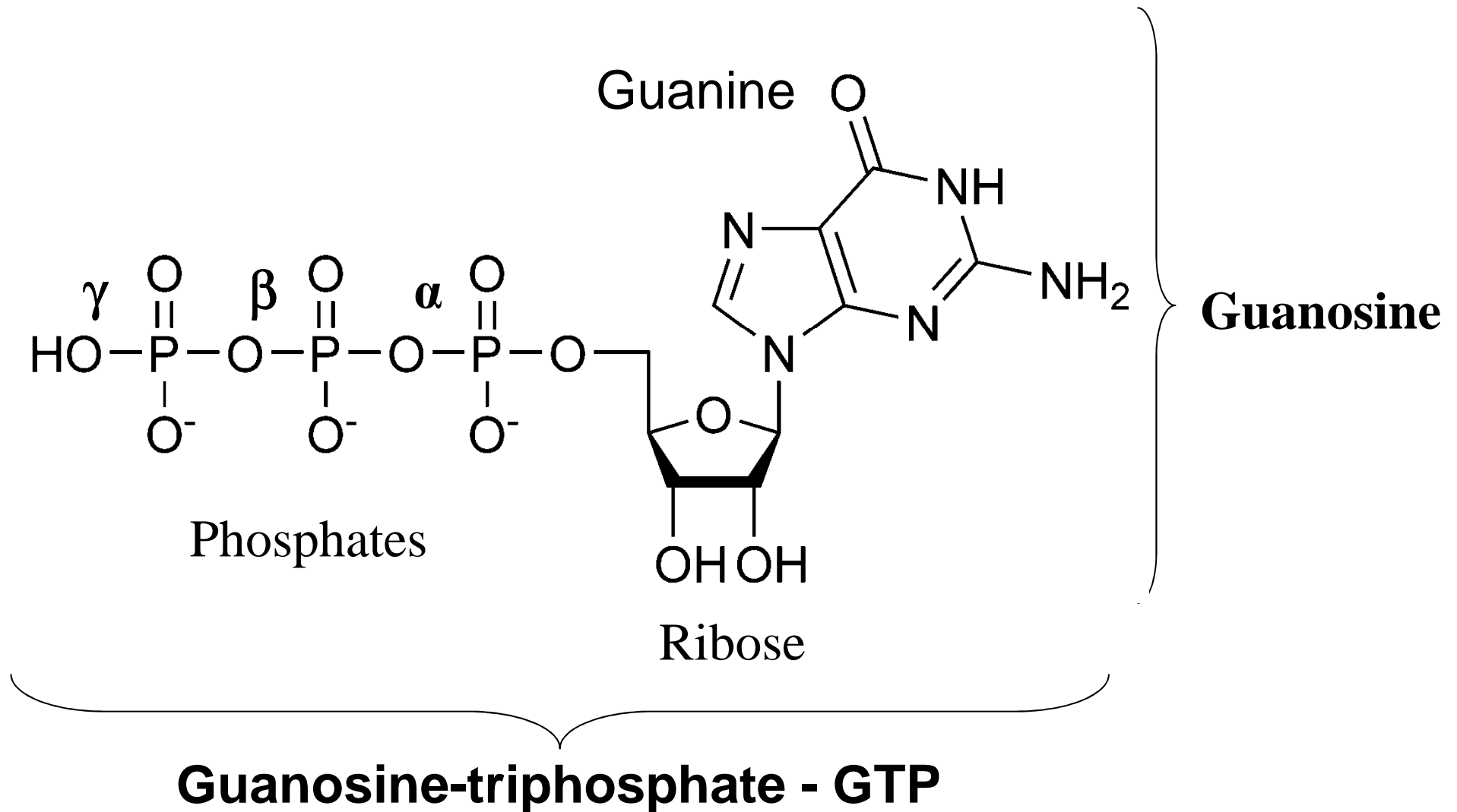
**1994 - Alfred Gilman and Martin Rodbell,  
Nobel Prize in Medicine for their discovery of  
G-Proteins and the role of these proteins in signal  
transduction in cells.**



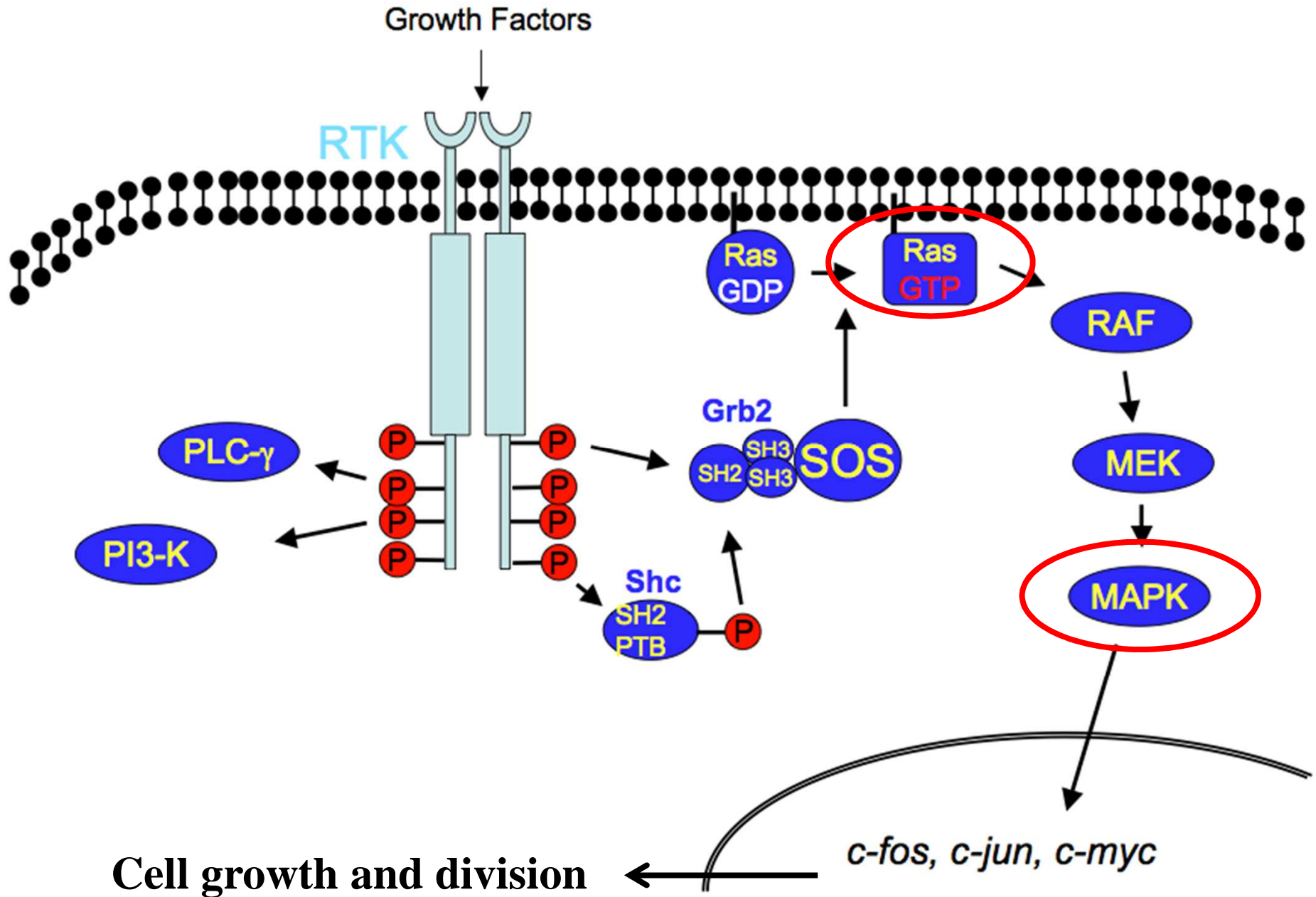
## **G-Protein families**

- **Heterotrimeric G-Proteins**, in 7-TM receptor signalling
- **Ras-like monomeric GTPases** (Ras, Rap, Rho, Ran, Rab, Arf, Arl, Sar), molecular switches in signal transduction
- **Initiation, elongation, termination factors** in protein synthesis (IF1, EF-Tu, EF-TS)
- **Tubulins**, members of a small family of globular proteins
- **Dynamin superfamily of GTPases**, remodelling of membranes

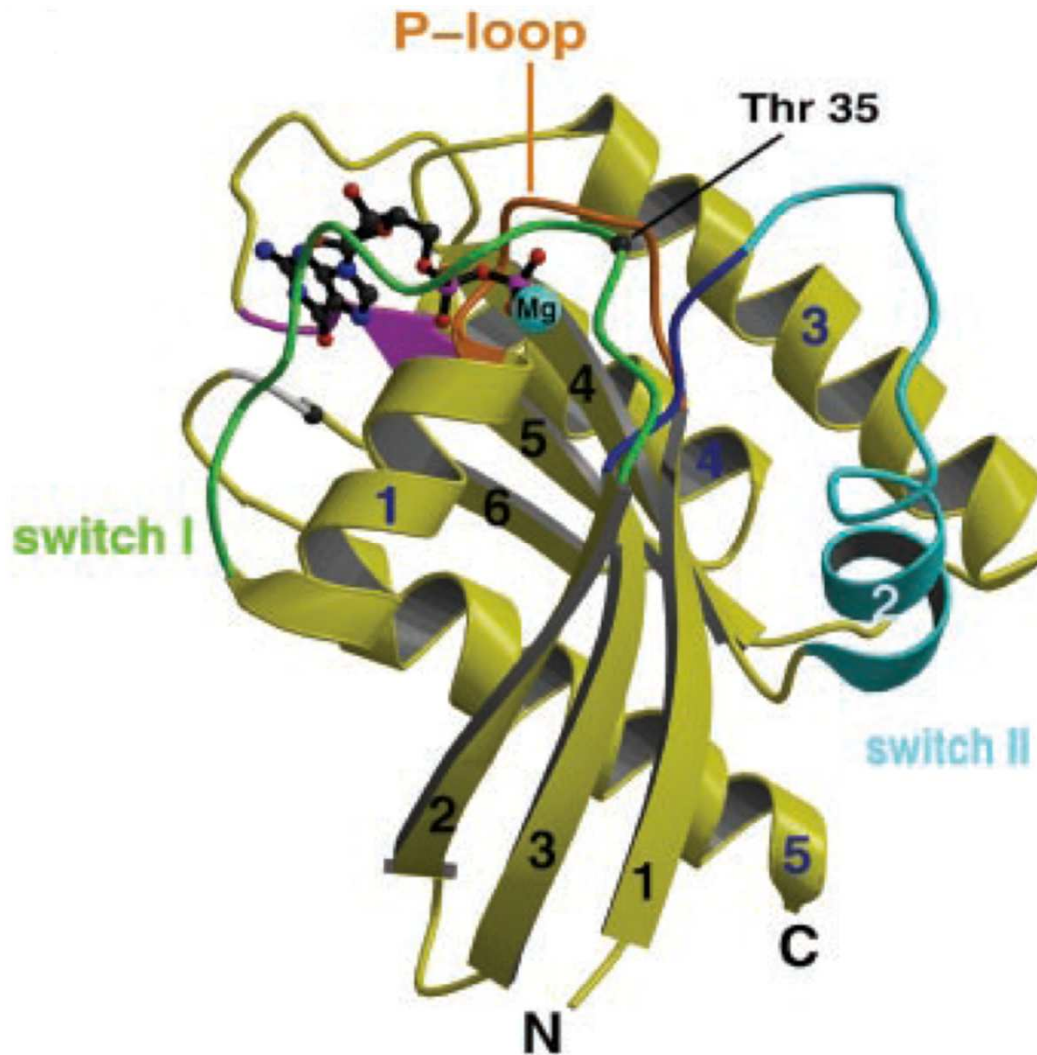
# G-Protein = Guanine-nucleotide binding protein (GNBP)



# Ras pathway



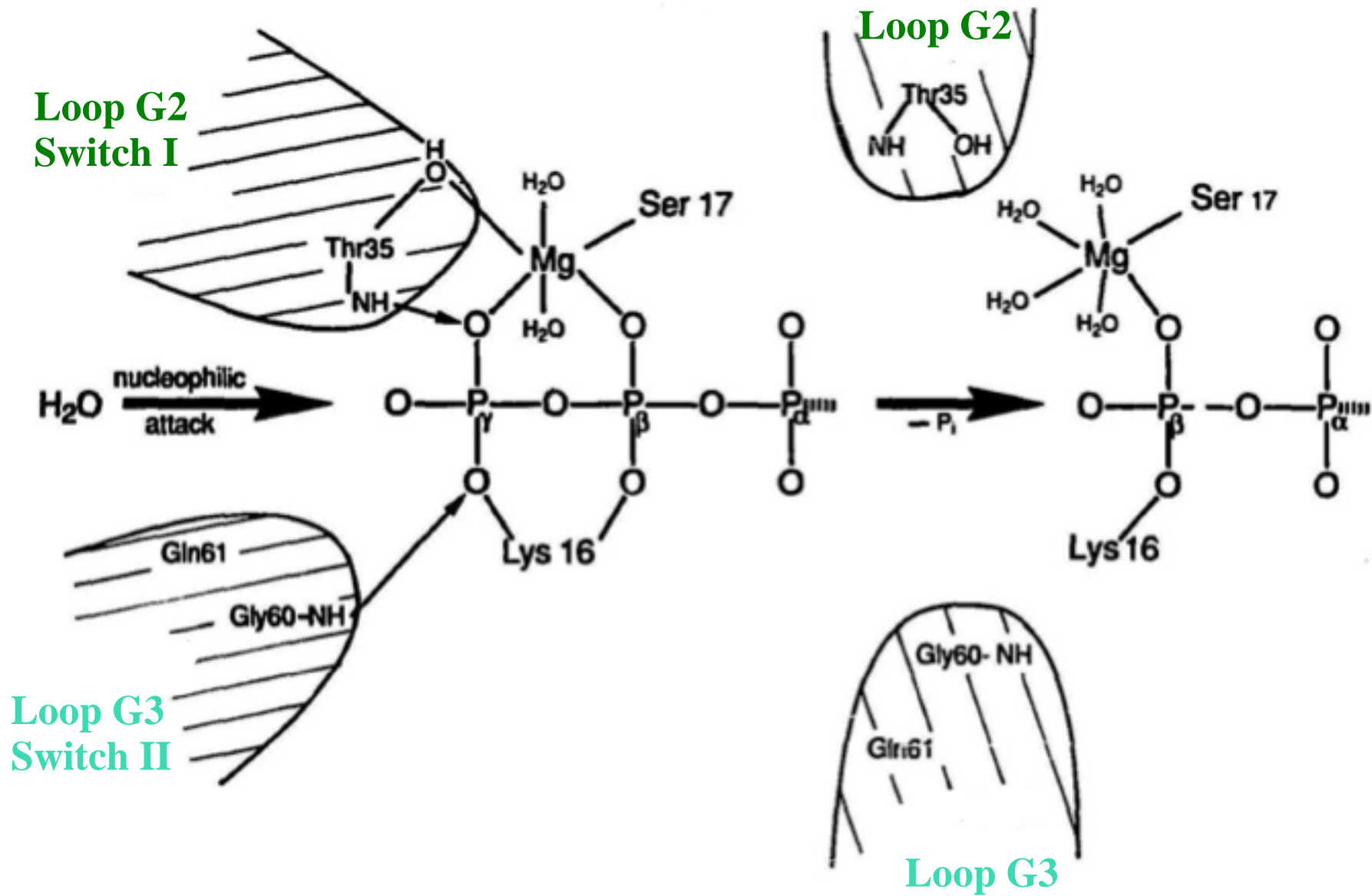
# Ras structure



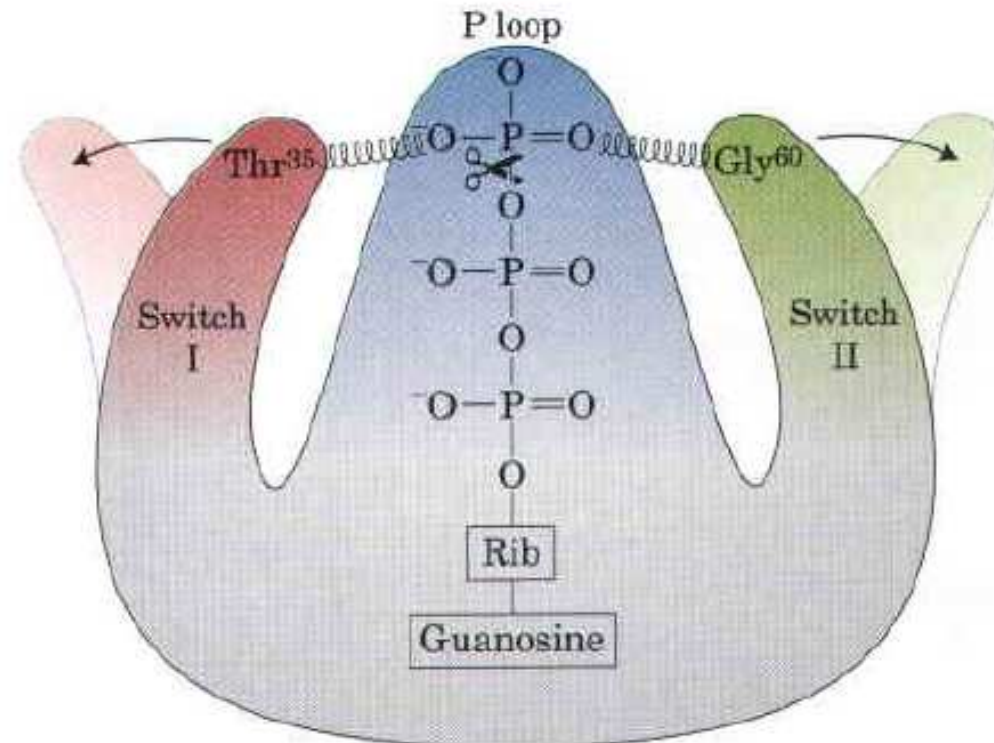
Ras has an  $\alpha/\beta$ -type structure in which the central  $\beta$  sheet comprises six  $\beta$  strands and five  $\alpha$  helices.

Loop regions form the GTP-binding site.

# The GTPase reaction



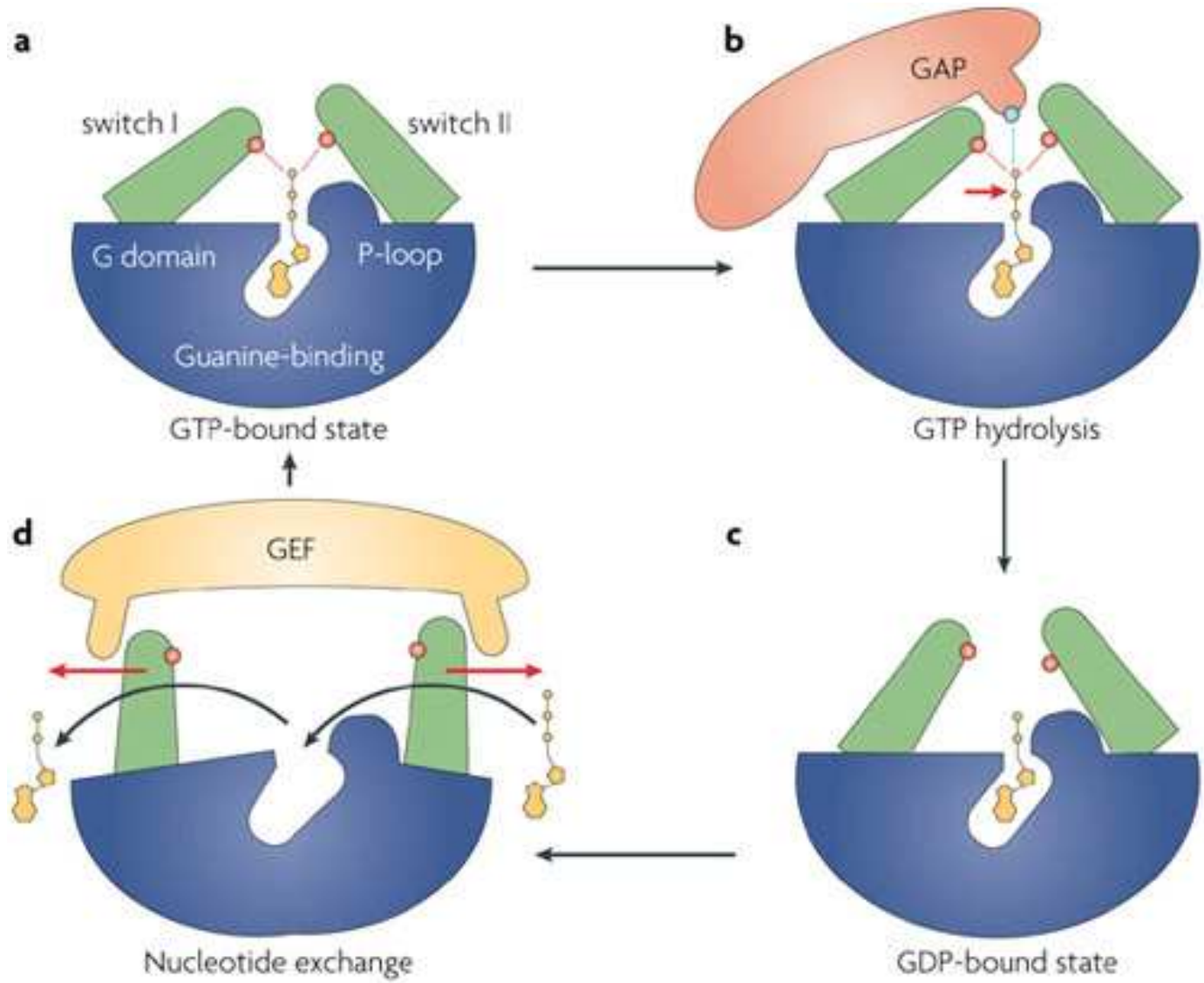
# The GTPase reaction



When bound GTP is hydrolyzed by the GTPase activities of Ras, loss of hydrogen bonds to Thr35 and Gly60 allows the switch I and switch II regions to relax into a conformation in which they are no longer available to interact with downstream targets such as Raf.

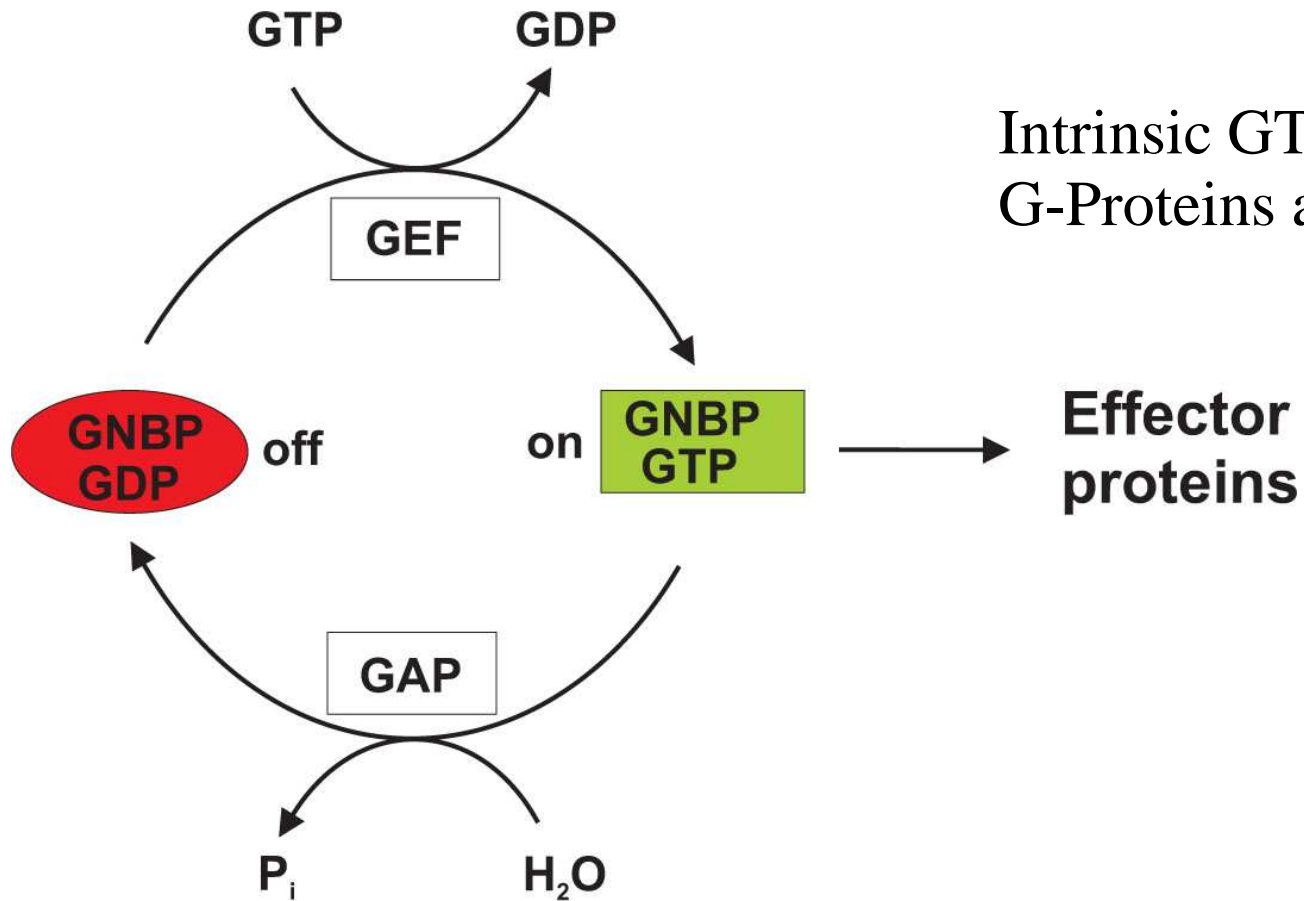


# Regulators of G-proteins activity



GEF: Guanine nucleotide Exchange Factor  
GAP: GTPase Activating Protein

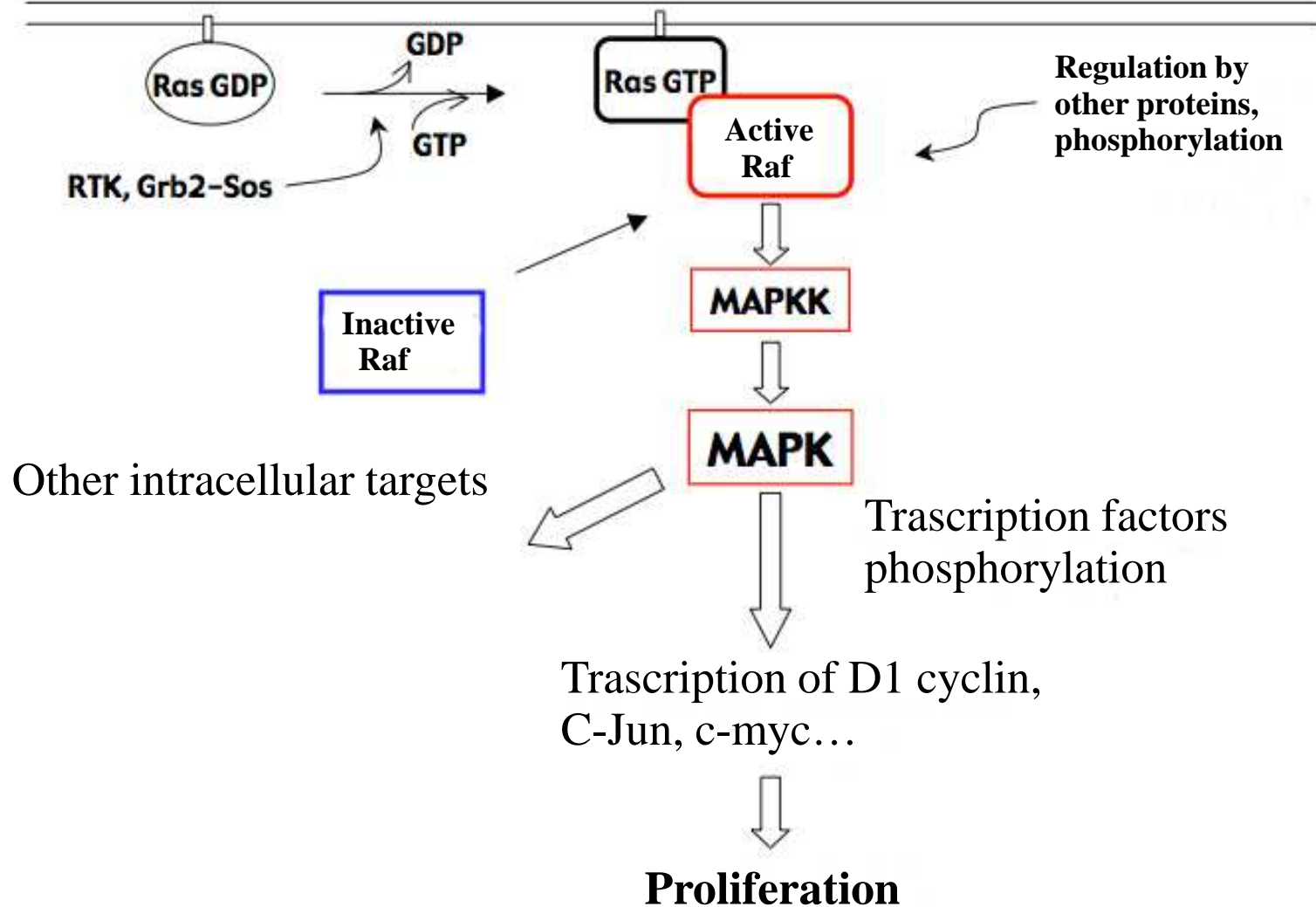
## Regulators of G-proteins activity 2



Intrinsic GTPase rates of small G-Proteins are slow

GEF: Guanine nucleotide Exchange Factor  
GAP: GTPase Activating Protein

# The importance of Ras as a molecular time-switches



MAPK = Mitogen Activated Protein Kinase

# G-protein: Binary switches in health and disease

Because G-proteins play crucial roles in so many signaling processes, it is not surprising that defects in G-proteins lead to a variety of disease:

- In about 25% of all **human cancer** there is a mutation in a Ras protein that virtually eliminates its GTPase activity
- “Activating” mutations in heterotrimeric G-proteins are found in about 40% of **pituitary tumors (adenomas)**
- Mutation in the gene for the transducin  $\alpha$  subunit ( $T\alpha$ ), which is involved in visual signaling, leads to a type of **night blindness**
- The pathogenic bacteria that cause **cholera** and **pertussis** produce toxins that target G proteins

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