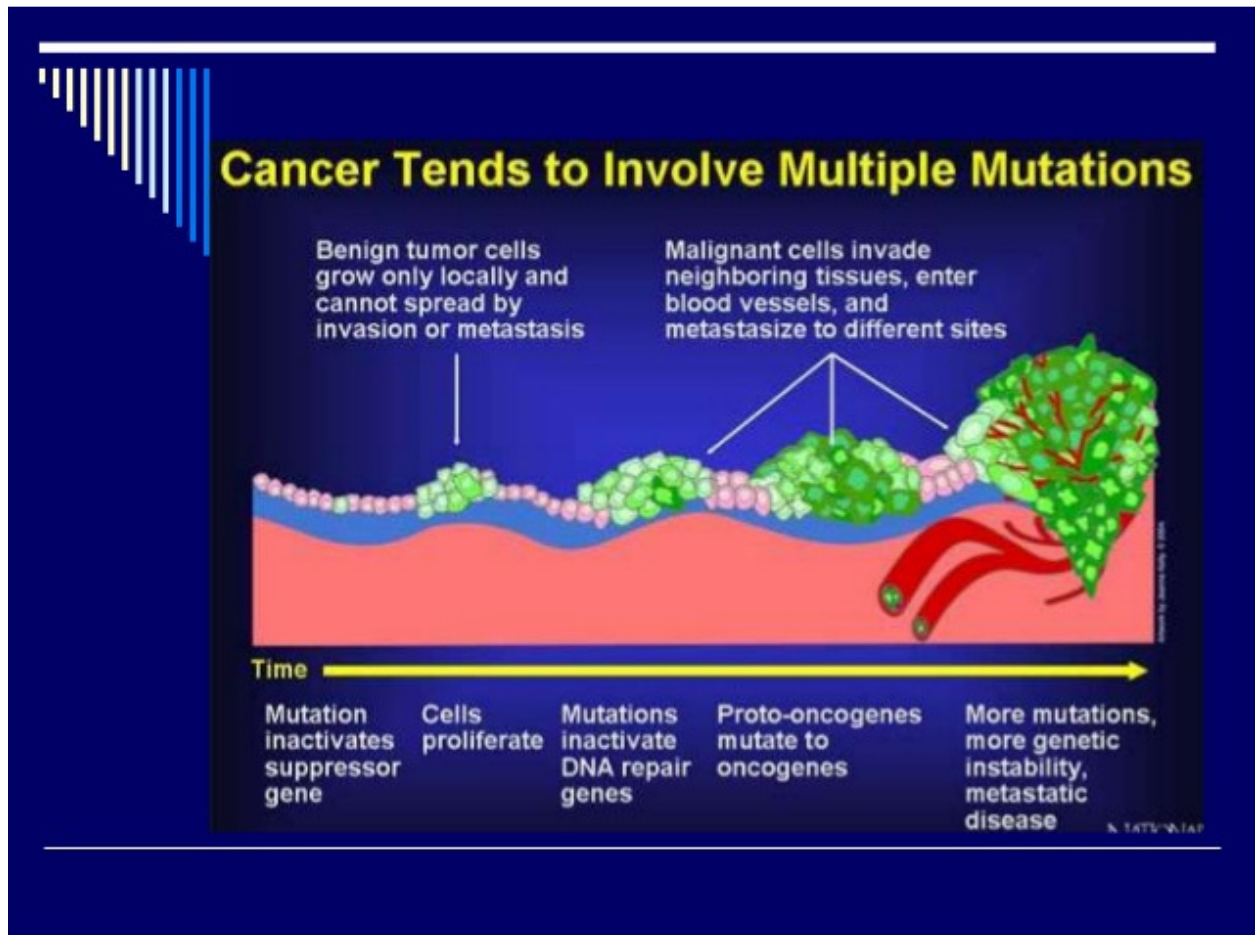
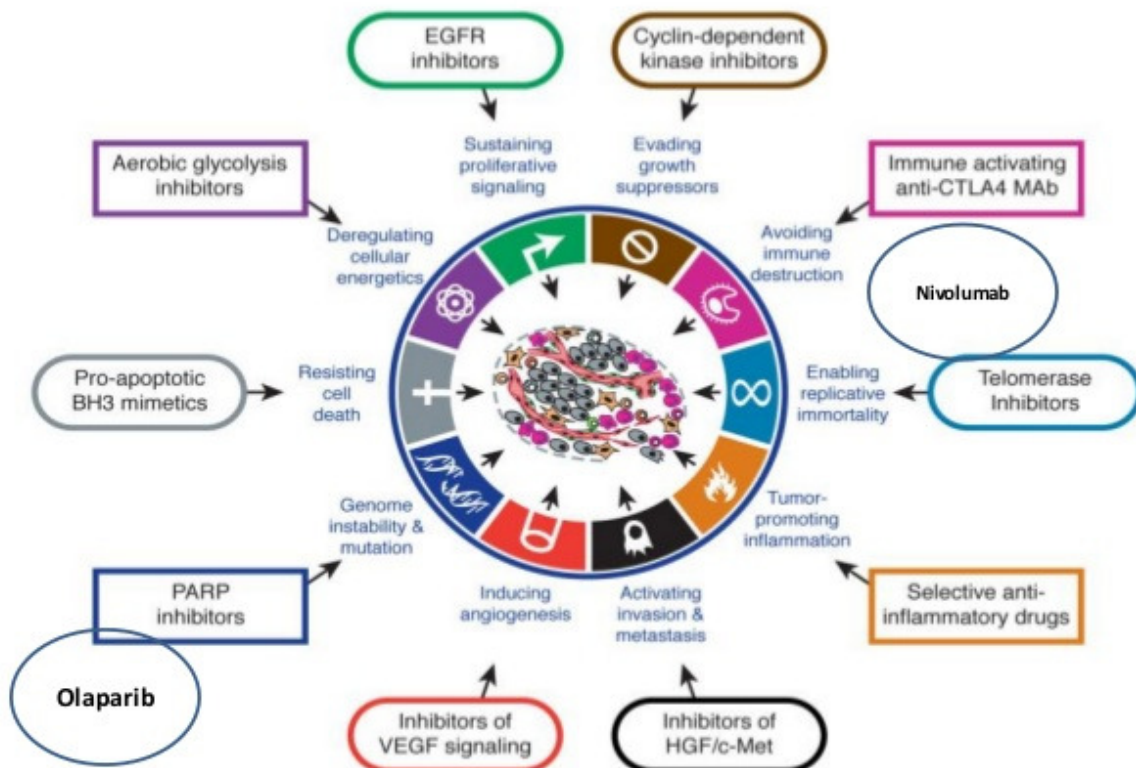


CANCER/ UG sem 2/SDG

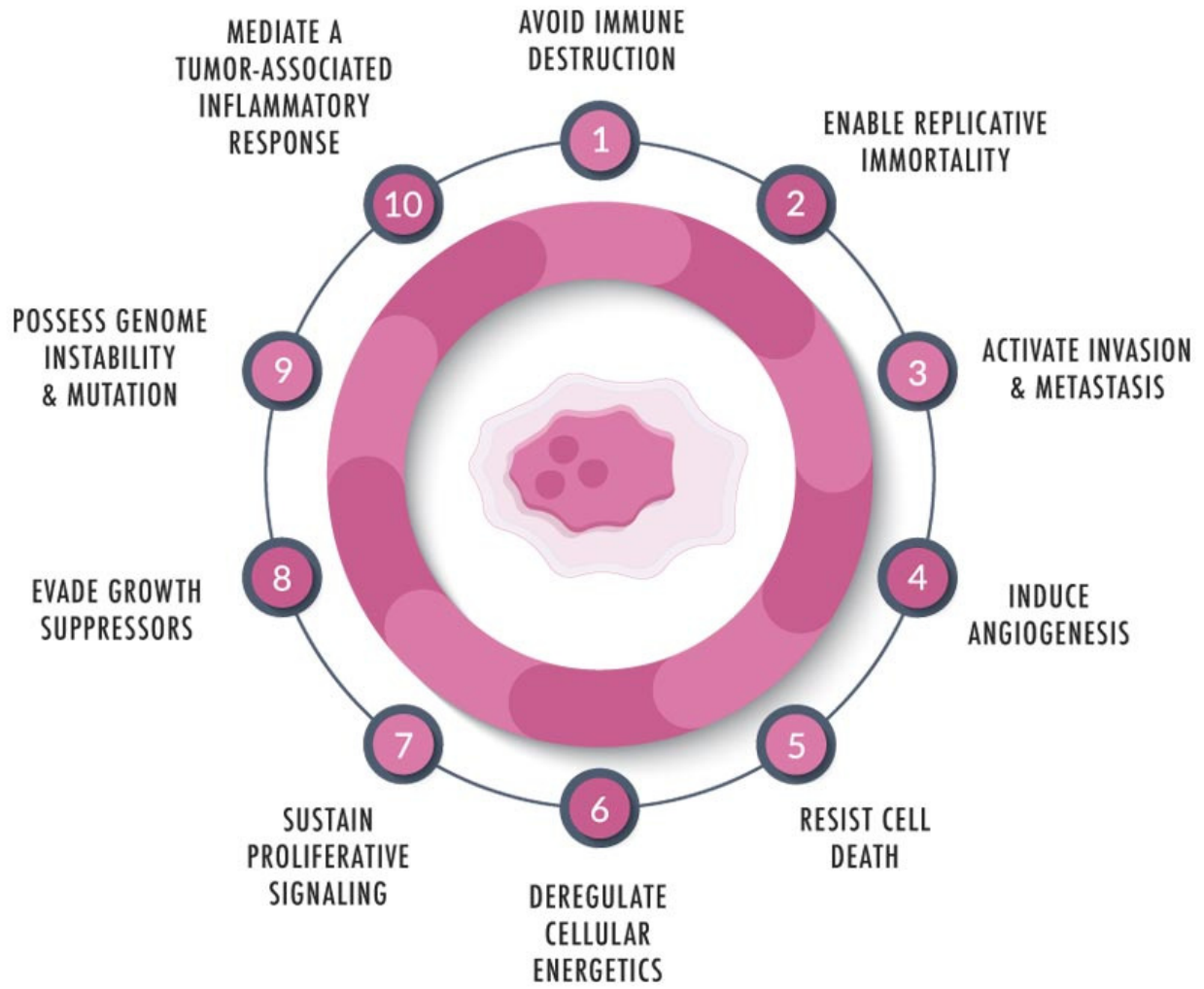




Hanahan and Weinberg, 2011



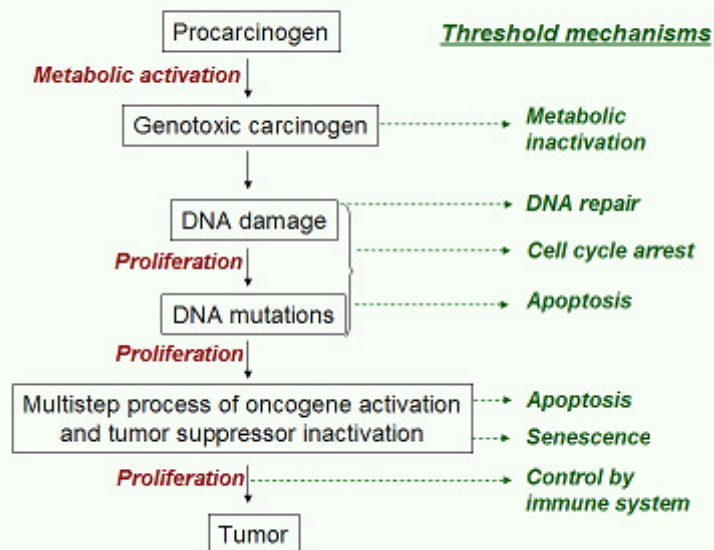
HALLMARKS OF CANCER



Hallmarks of Cancer

- Sustaining proliferative signaling,
- Evading growth suppressors
- Resisting cell death
- Enabling replicative Immortality
- Inducing angiogenesis
- Activating invasion and metastasis
- Deregulating cellular energetics
- Evading immune destruction

Multistep Process of Carcinogenesis



From: Hengstler, Bogdanffy, Bolt and Oesch,
Annu Rev Pharmacol Toxicol. 2003;43:485-520

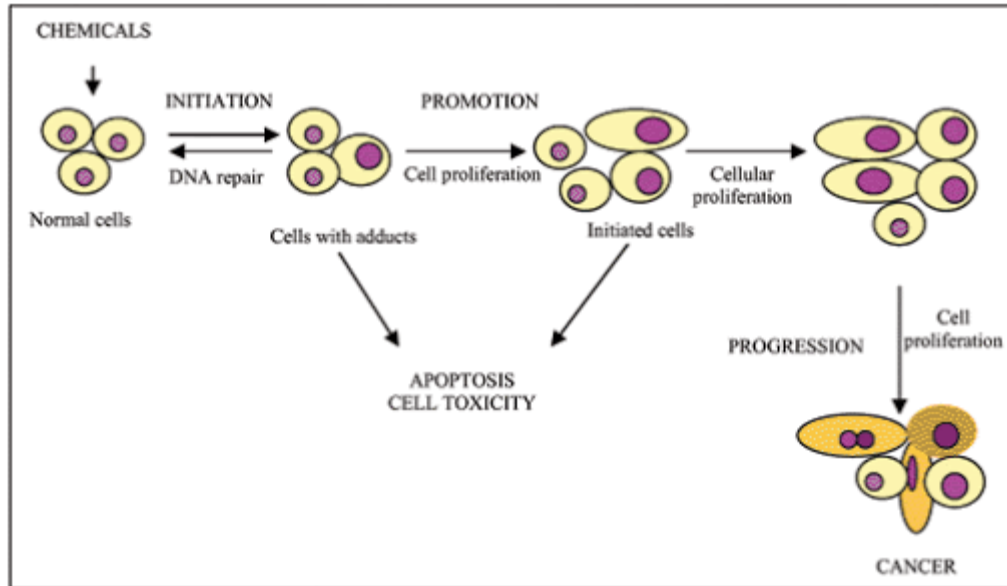


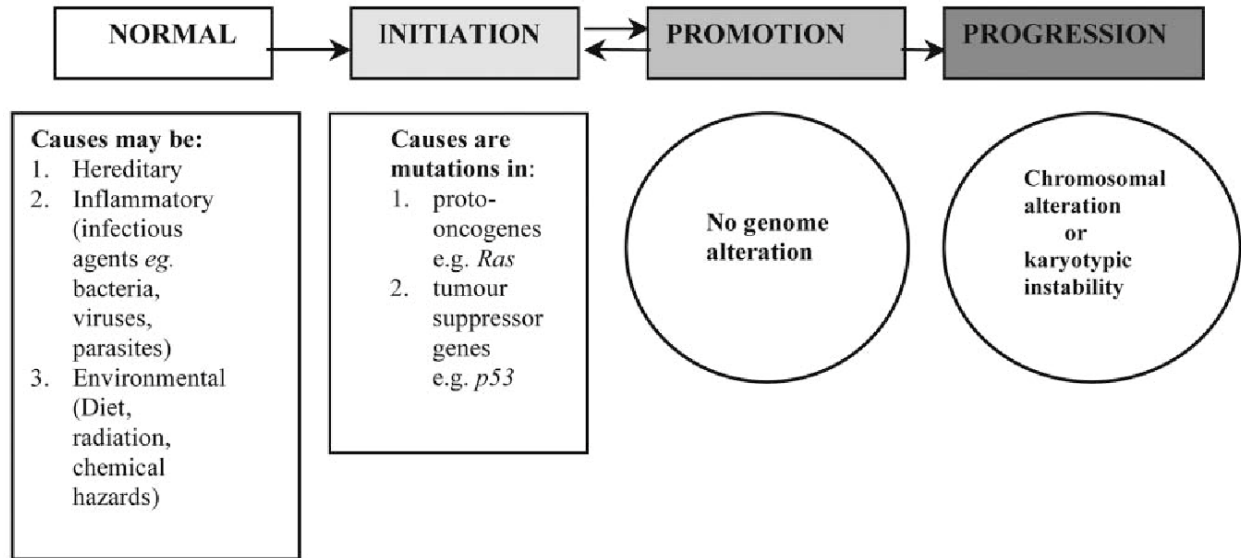
Fig. 2 – Chemical carcinogenesis stages and the occurrences involved in each one.

Different Steps of Carcinogenesis

Initiation: Mutation in one or more cellular genes controlling key regulatory pathways of the cell (irreversible)—must be a heritable DNA alteration.

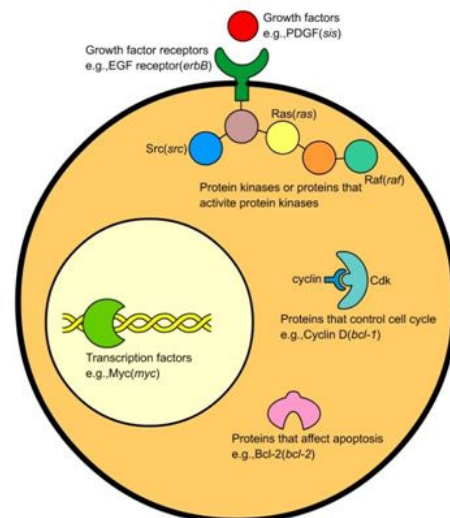
Promotion: selective growth enhancement induced in the initiated cell and its progeny by the continuous exposure to a promoting agent.

Progression: results from continuing evolution of unstable chromosomes; further mutations from genetic instability during promotion—results in further degrees of independence, invasiveness, metastasis, etc.



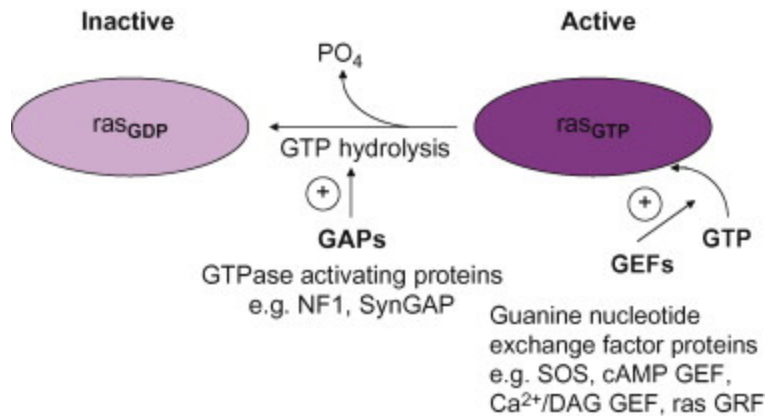
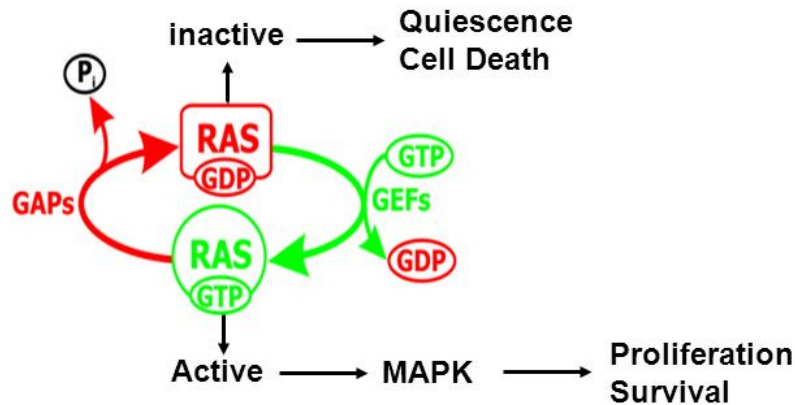
ras proto-oncogene:

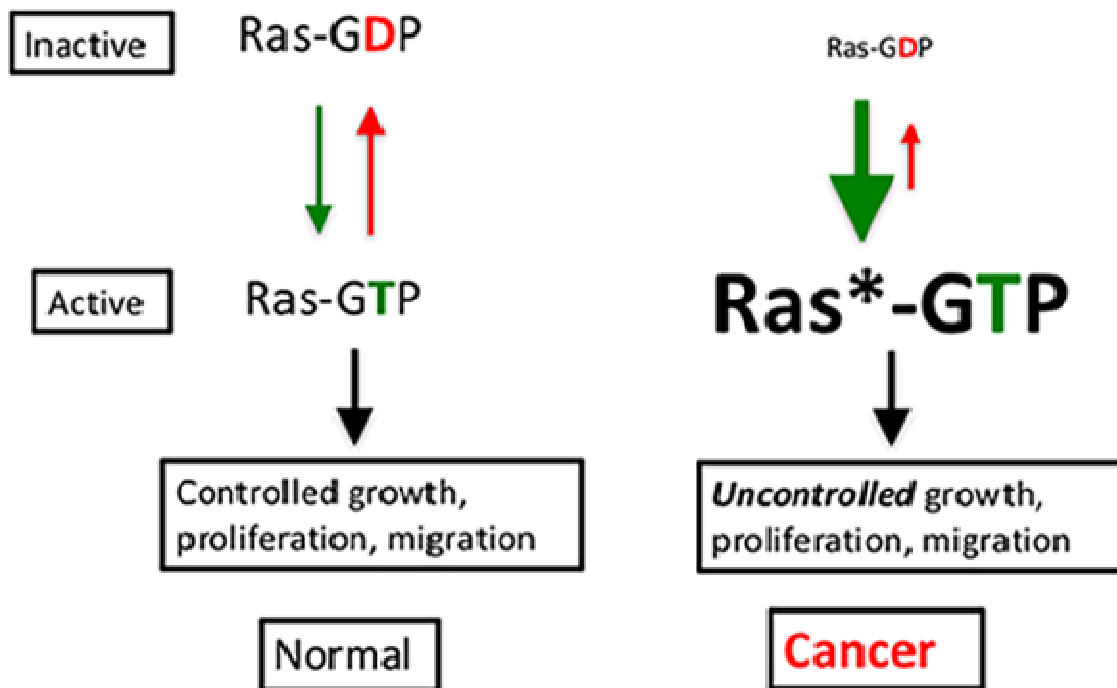
- mutations in the **ras gene** are found in about 30% of human cancers
- the product is the **Ras protein**
- the **Ras protein** is a G protein that relays a growth signal from a growth factor receptor on the plasma membrane to a cascade of **protein kinases**



RAS, the most frequently mutated or activated oncogene in human cancer

- Three Ras isoforms: H-ras, K-ras, and N-ras
- Mutated in 20-25% of tumors (G12D) but over 90% in pancreatic cancer
- Mutations also common in colorectal and NSCLC
- Ras switches between active and inactive conformations.
- Ras mutations inhibit Ras GTPase activity thus locking it permanently in the active state.





- Ras is a GTP-binding protein and is the most widely studied oncoprotein.
- To achieve its biological activity, it must undergo post-translation modification. Ras acts as a typical molecular switch.
- The GTP-bound Ras can activate several downstream effector pathways. Ras signaling regulates many important physiologic processes within a cell, such as cell cycle progression, survival, apoptosis, etc.
- Several studies have found mutation in Ras or its effectors in various types of tumors.
- Therefore, Ras or its downstream effectors can be attractive drug targets against various types of tumors in cancer therapeutics.

RAS Signaling

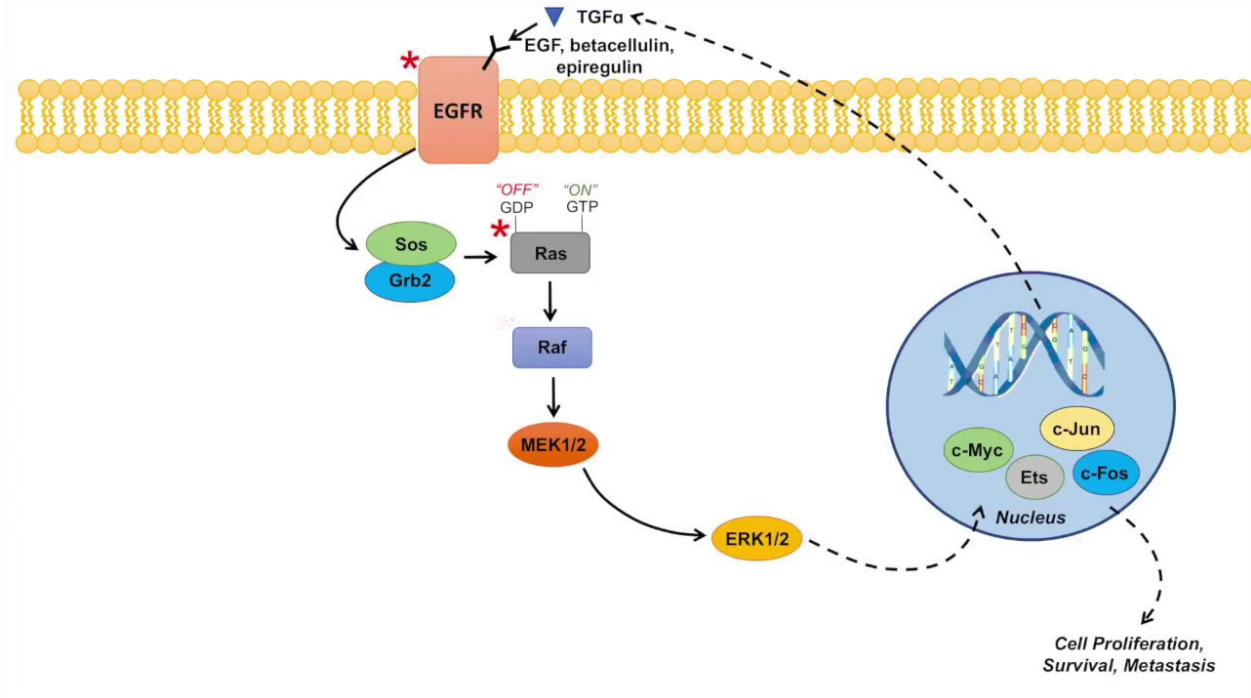
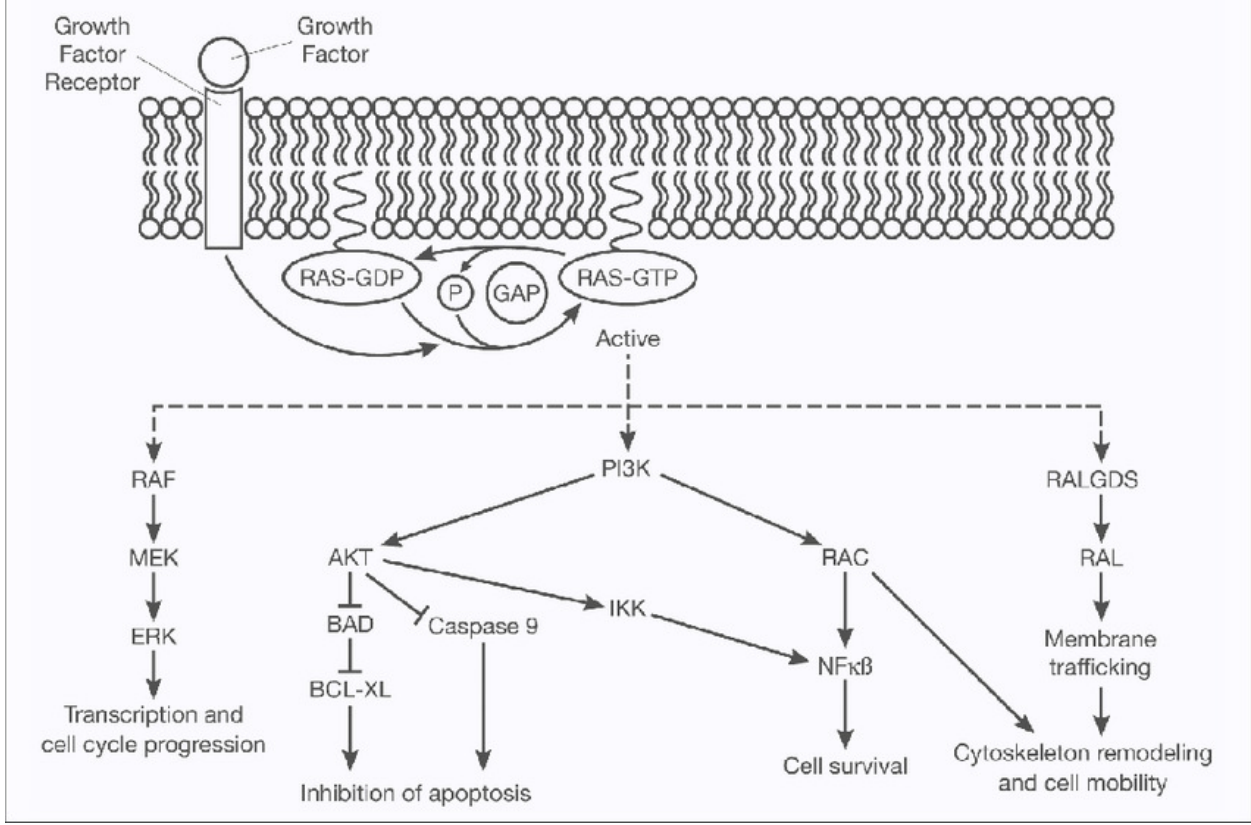


Figure 4: Four Categories of Ras Inhibition Strategies

