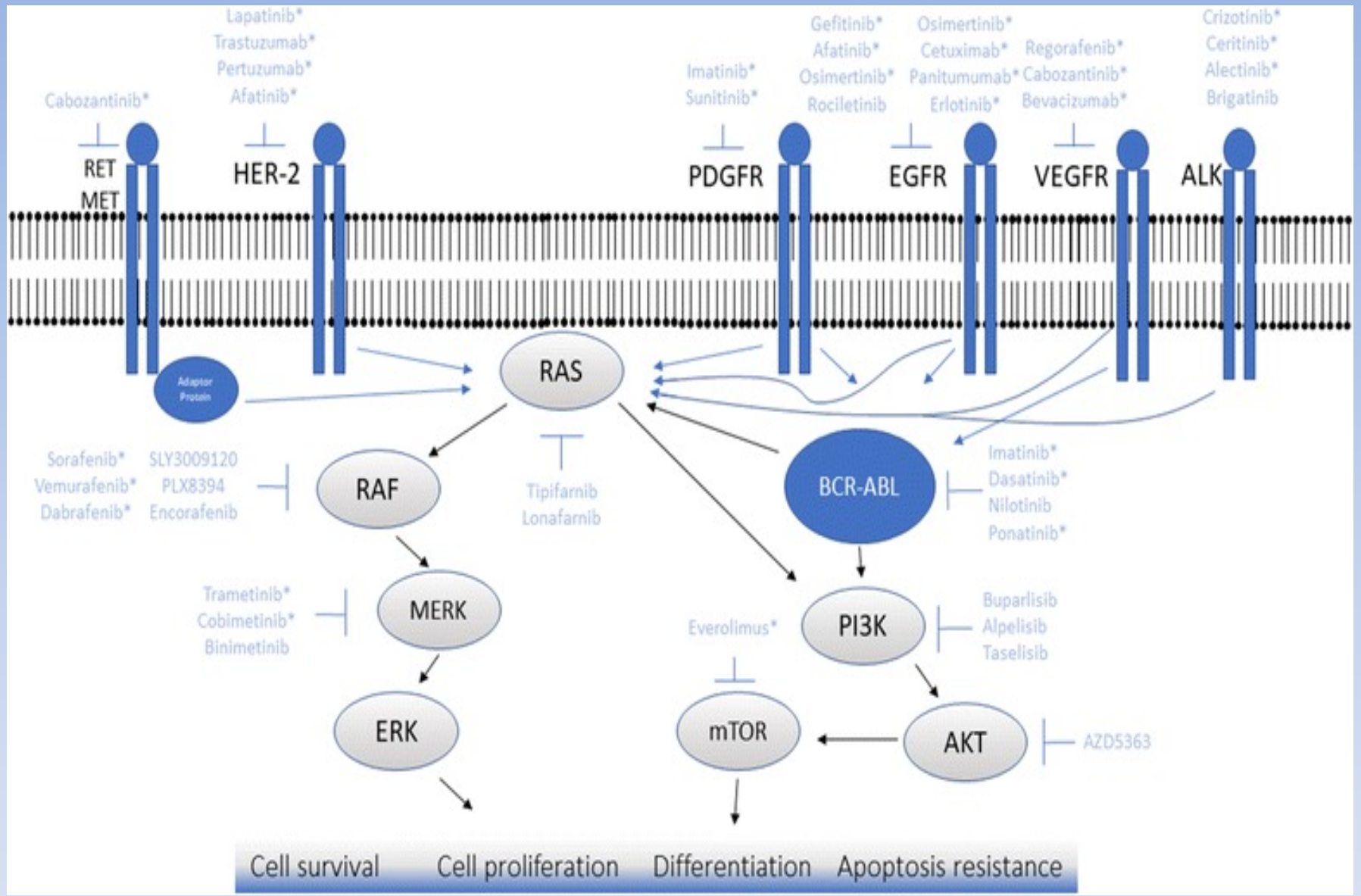
Receptor tyrosine kinases (RTKs)

Prof.Dr.Nuray ARI, 2018

- **RTKs, being membrane anchored, indirectly send signals to the cell nucleus through cytoplasmic pathways involving a series of molecules that eventually culminate with translocation of specific proteins from the cytoplasm activating and/or acting as transcription factors orchestrating proliferation through gene expression**

Mol Cancer. 2018,17(1):55. Tyrosine kinases and downstream pathways as druggable targets for cancer treatment: the current arsenal of inhibitors.Montor WR, Salas AROSE, Melo FHM.



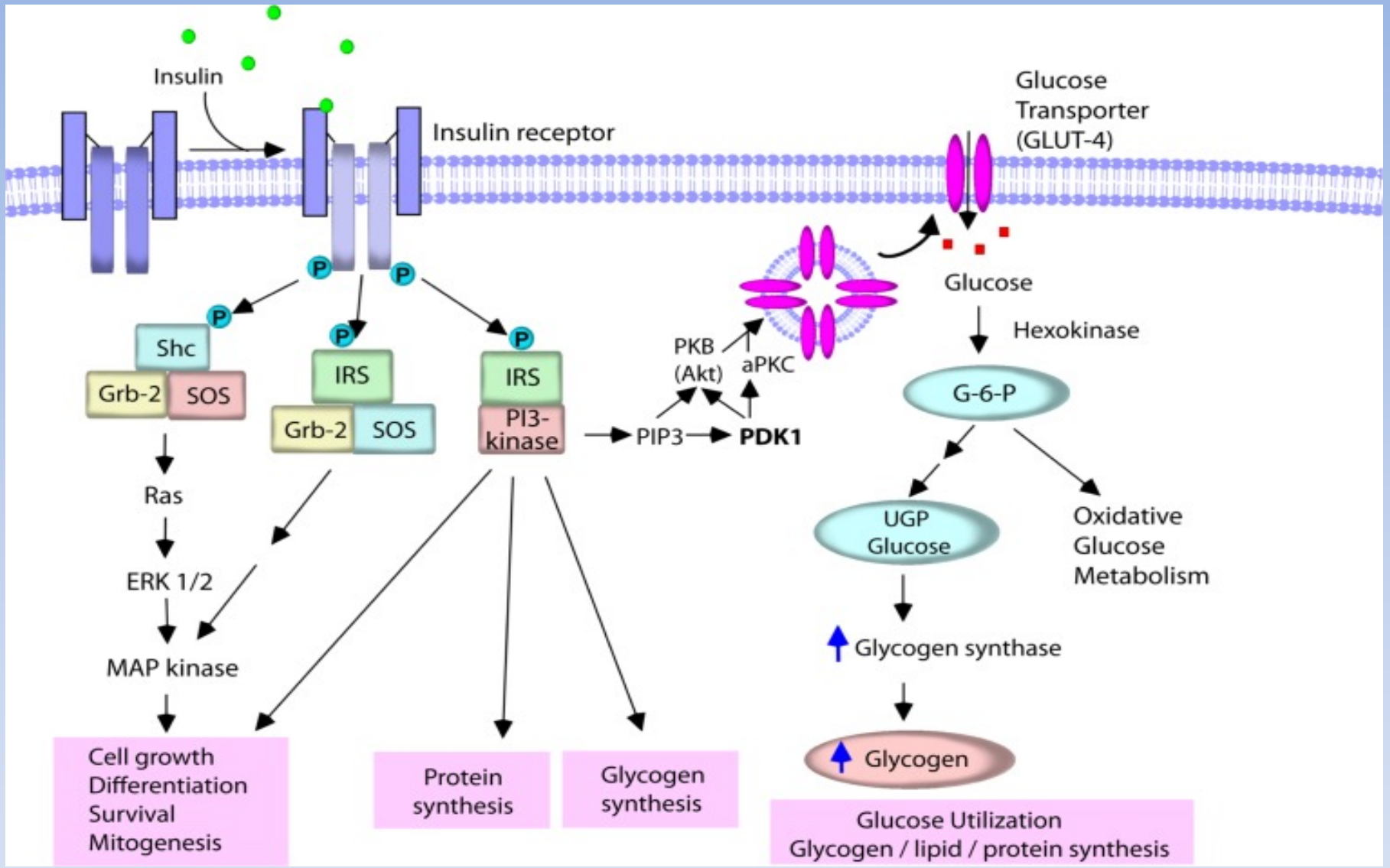
Examples of druggable targets and their inhibitors.

Mol Cancer. 2018 Feb 19;17(1):55. tyrosine kinases and downstream pathways as druggable targets for cancer treatment: the current arsenal of inhibitors.Montor WR, Salas AROSE, Melo FHM.

- **Receptor tyrosine kinases and downstream pathways as druggable targets for cancer treatment: the current arsenal of inhibitors.**

- Mol Cancer. 2018 Feb 19;17(1):55. doi: 10.1186/s12943-018-0792-2.Montor WR[1], Salas AROSE[1], Melo FHM[2].

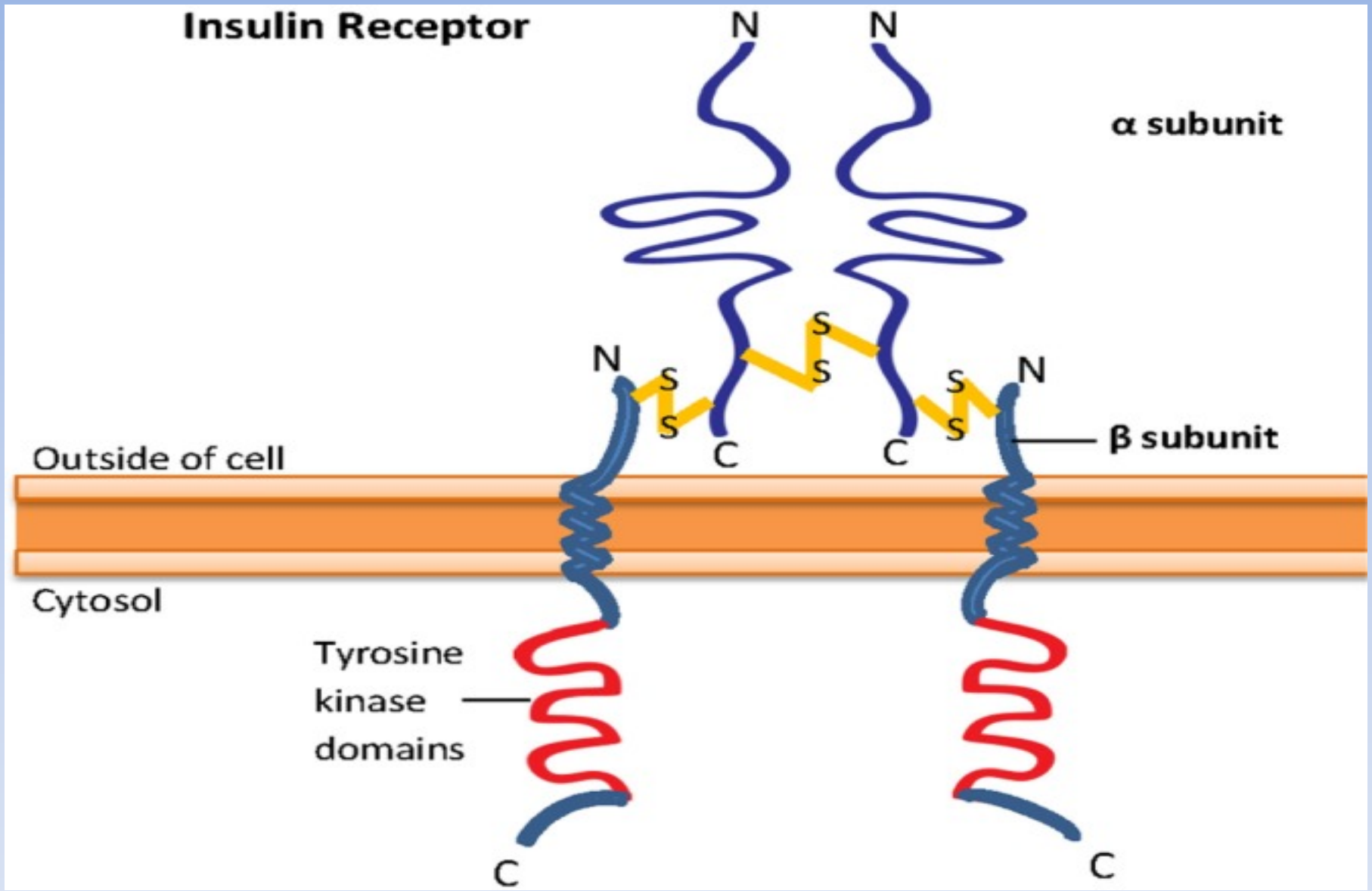
- **Abstract**
- **Searching for targets that allow pharmacological inhibition of cell proliferation in over-proliferative states, such as cancer, leads us to finely understand the complex mechanisms orchestrating the perfect control of mitosis number, frequency and pace as well as the molecular arrangements that induce cells to enter functional quiescence and brings them back to cycling in specific conditions. Although the mechanisms regulating cell proliferation have been described several years ago, never before has so much light been shed over this machinery as during the last decade when therapy targets have been explored and molecules, either synthetic or in the form of antibodies with the potential of becoming cancer drugs were produced and adjusted for specific binding and function. Proteins containing tyrosinekinase domains, either membrane receptors or cytoplasmic molecules, plus the ones activated by those in downstream pathways, having tyrosine kinase domains or not, such as RAS which is a GTPase and serine/threonine kinases such as RAF, play crucial role in conducting proliferation information from cell surroundings to the nucleus where gene expression takes place. Tyrosine kinases phosphorylate tyrosine residues in an activating mode and are found in important growth factor receptors, such as for ligands from families collectively known as VEGF, PDGF and EGF, to name a few and in intracellular downstream molecules. They all play important roles in normal physiology and are commonly found mutated or overexpressed in neoplastic states. Our objective here is to present such kinases as druggable targets for cancer therapy, highlighting the ones for which the pharmacological arsenal is available, discussing specificity, resistance mechanisms and treatment alternatives in cases of resistance, plus listing potential targets that have not been successfully worked yet.**



Insulin signaling pathway .

β-Adrenergic Receptor and Insulin Resistance in the Heart.

Biomol Ther (Seoul). 2017 Jan 1;25(1):44-56. doi: 10.4062/biomolther.2016.128. Mangmool S



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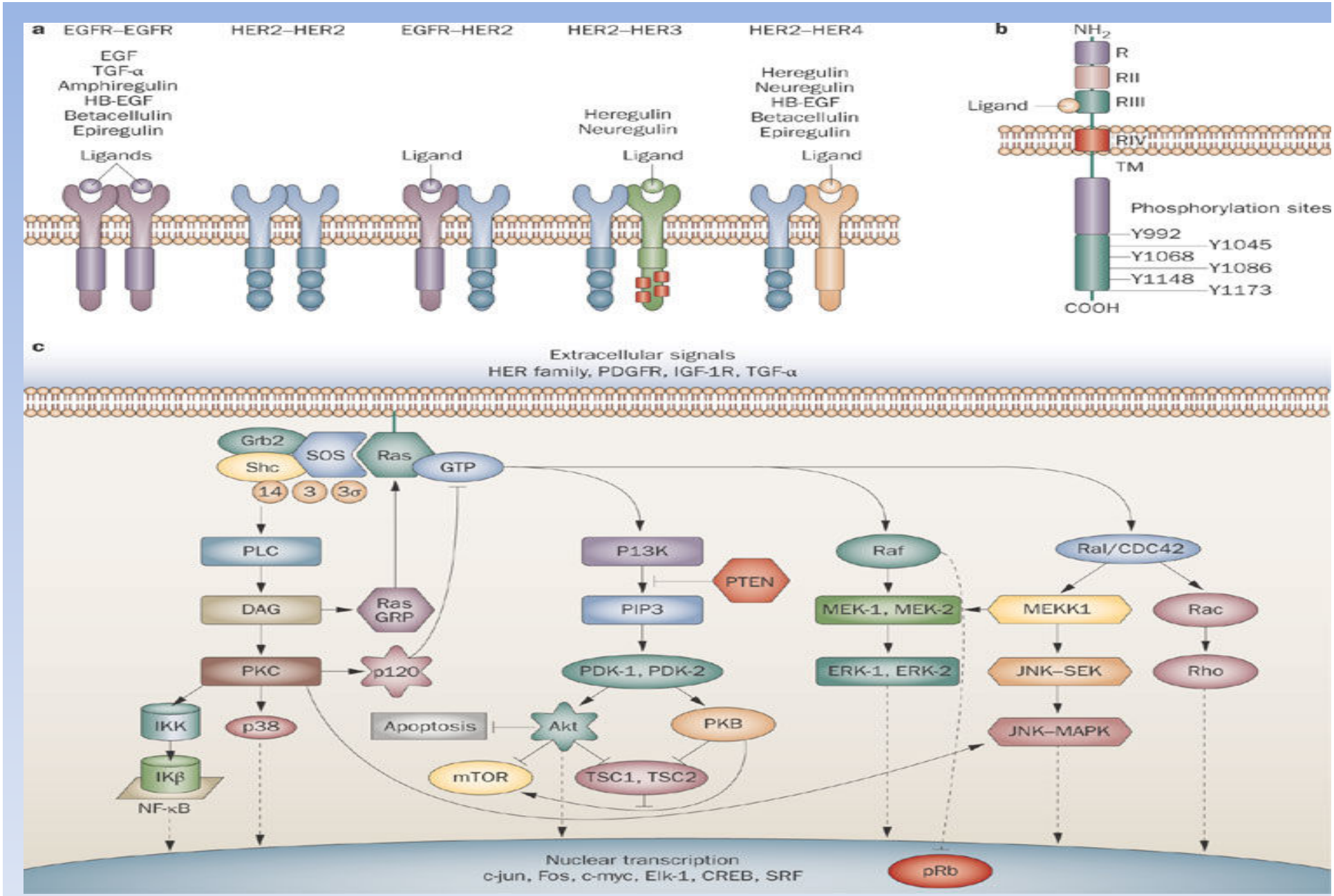
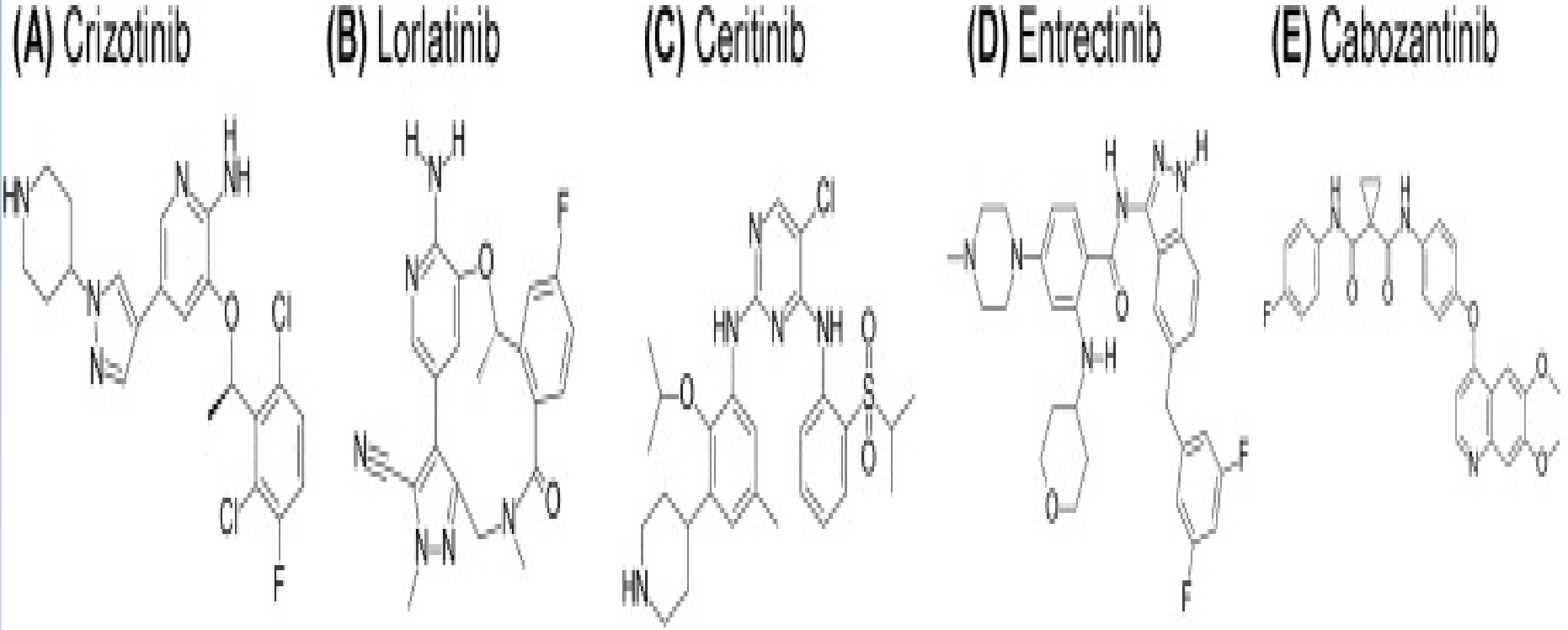


http://free-stock-illustration.com/tyrosine+kinase+receptor+inhibitors?image=12534843

ROS1

ROS1 is a so-called orphan receptor protein-tyrosine kinase because no activating ligand has (yet) been identified. In part because of the absence of a known activating ligand, the physiological functions of ROS1 are unknown. This receptor is in various tissues and organs during embryonic development but with little expression in adults. Of some two dozen adult human tissues studied, the highest expression level (although slight) occurs in lung followed by cervix and colon. Oncogenic activation of ROS1 as a result of chromosomal rearrangements has been reported in patients with non-small cell lung cancer, glioblastoma, cholangiocarcinoma, ovarian carcinoma, angiosarcoma, inflammatory myofibroblastic tumors , and Spitzoid melanocytic tumors .

Pharmacol Res. 2017 Jul;121:202-212. doi: 10.1016/j.phrs.2017.04.022. Epub 2017 Apr 30. ***ROS1 protein tyrosine kinase inhibitors in the treatment of ROS1 fusion protein-driven non-small cell lung cancers.*** *Roskoski R Jr.*



Structures of selected ROS1 inhibitors.

Pharmacol Res. 2017 Jul;121:202-212. doi: 10.1016/j.phrs.2017.04.022. Epub 2017 Apr 30. ***ROS1 protein-tyrosine kinase inhibitors in the treatment of ROS1 fusion protein-driven non-small cell lung cancers.*** *Roskoski R Jr.*

Tyrosine kinase inhibitors

- ATP-binding cleft is the target for rationally designed small molecules **TK inhibitors**
- Structural analogue of ATP
- e.g. Imatinib (Glivec, bcr-abl inhibitor)
- *Flavonoids* are naturally occurring ATP analogues
- Targeting angiogenesis (gefitinib, EGFR inhibitor)
- Non-specific interactions are possible
- Multi-kinase inhibitor: sunitinib
  - VEGFR, Flt-3, PDGFR, c-kit, stem-cell factor receptor, Fms-like RTK3.
- **Monoclonal Ab** target the extracellular ligand binding domain
  - Herceptin (trastuzumab)
  - Cetuximab (EGFR)

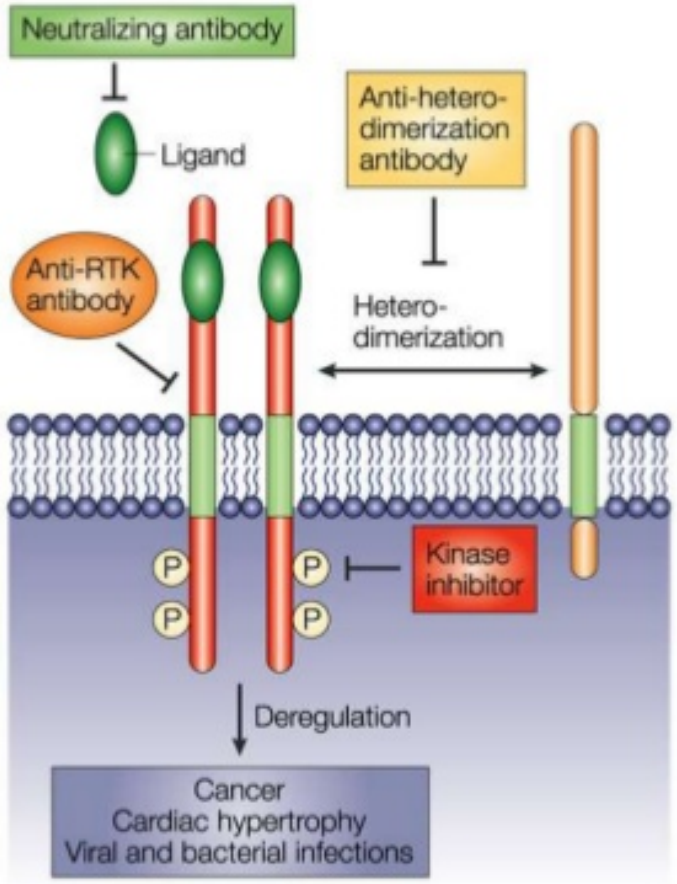


Table 1. Summary of EGFR Inhibitors

Drug	Class	Cancer Indication	Dosage[a]	Adverse Reactions[b]
Afatinib (Gilotrif)	TKI	NSCLC	40 mg/day po	Cutaneous (alopecia, hair changes, hyperpigmentation, nail changes, pruritus, rash, xerosis); diarrhea (po agents); electrolyte disorders (hypomagnesemia, hypocalcemia); ocular (conjunctivitis, dry eye, eyelid dysfunction); liver dysfunction (erlotinib, gefitinib, lapatinib [BBW]); pulmonary dysfunction (interstitial disease); cardiotoxicity (lapatinib); infusion reactions (cetuximab, panitumumab)
Erlotinib (Tarceva)	TKI	NSCLC, pancreatic	100-150 mg/day po	
Gefitinib (Iressa)	TKI	NSCLC	250 mg/day po	
Lapatinib (Tykerb)	TKI	Breast HER2+	1,000-1,500 mg/day po	
Vandetanib (Caprelsa)	TKI	MTC	300 mg/day po	
Cetuximab (Erbitux)	Mab	Colorectal, head and neck, NSCLC, skin	400 mg/m^2 (loading), then 250 mg/m^2/wk IV infusion (maintenance); or 500 mg/m^2 IV infusion q2w (colorectal)	
Panitumumab (Vectibix)	Mab	Colorectal	6 mg/kg IV infusion q2w	

[a] *Varies by indication.*
[b] *For entire class (exceptions noted). List is not all-inclusive.*
BBW: black box warning; EGFR: epidermal growth factor receptor; HER2+: human epidermal growth factor receptor 2–positive; Mab: monoclonal antibody; MTC: medullary thyroid carcinoma; NSCLC: non–small cell lung cancer; TKI: tyrosine kinase inhibitor.
Source: Reference 3.

https://www.uspharmacist.com/article/epidermal-growth-factor-receptor-inhibitors-and-skin-rash