National and Kapodistrian University of Athens
Medical School
Department of Biological Chemistry

Biochemistry

Lecture:

Carcinogenicity and cell signaling

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Why Signal Transduction/Cell Signaling Is Important in Cancer?

Cell signaling regulates:

- ❑ cell cycle and proliferation,
- ❑ migration,
- ❑ differentiation,
- ❑ viability versus cell death,
- ❑ metabolism, etc.

Deregulation of cell signaling impacts cellular homeostasis

Aberrant, constitutive activation of a proliferation promoting pathway

selective advantage of the cell

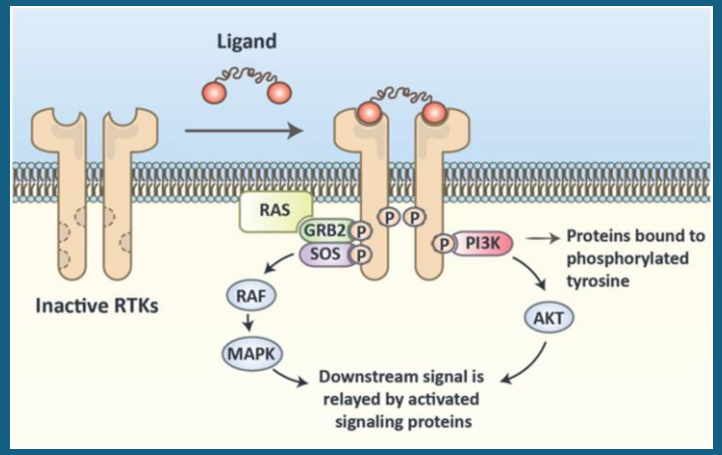
clonal expansion

Signaling players are often oncogenes (or, sometimes, tumor suppressors)

-> the first human proto-oncogene to be cloned, RAS, mutated in 30% of cancers

Key Signaling Pathways in Cancer

Pathways	Activated by	Involved	Available clinical drugs (some..)
Ras/MAPK	Cytokines and mitogenic growth factors	Melanoma; thyroid, pancreatic and NSCL cancers	Vemurafenib; Trametinib
PI3K/Akt/mTOR	Insulin; growth factors; chemokines	Glioblastoma; breast, prostate, colon and endometrial cancer	Buparlisib; MK-2206; rapamycin; BEZ-235
JAK/STAT	Cytokines (e.g. IL-3, IL-6 and IL-7)	Myeloproliferative neoplasms; breast and prostate cancers	Ruxolitinib; Tofacitinib
Nuclear hormone receptor	Steroid hormones (e.g. estrogen and progesterone)	Breast and prostate cancers	Tamoxifen; enzalutamide
Notch	Delta-like (DLL) 1, 3 and 4; Jagged (JAG) 1 and 2	T-ALL; CLL; MCL; breast adenocarcinoma; SCC	γ-secretase inhibitors (RO4929097)
Wnt (β-catenin)	Wnt ligands	Melanoma; breast and colorectal cancers	LGK974; PRI-724
TGF-β (Smad)	TGF-β	Prostate, breast and pancreatic cancers	Fresolimumab; Galunisertib
NF-κB	Cytokines (e.g. TNF-α; IL-l)	Breast cancer; B-cell lymphomas; multiple myeloma	Bortezomib
Hippo	DCHS1, DCHS2	Breast cancer; familial and sporadic schwannomas	Verteporfin; Dobutamine
Hedgehog	Sonic (SHH), Indian (IHH), or desert (DHH) hedgehog	Glioblastoma; basal cell carcinoma; medulloblastoma; CML	IPI-926; Vismodegib
DNA repair signaling (ATM/ATR)	Single-stranded DNA (ssDNA) and DNA double-strand breaks (DSBs)	Breast, colorectal and lung cancers	Olaparib; MK-8776



RTK stands for **Receptor Tyrosine Kinase** — a type of **cell surface receptor** that plays a crucial role in **cell signaling**.

Βασικά χαρακτηριστικά των RTK:

Βρίσκεται στην κυτταρική μεμβράνη

Ενεργοποιείται από συνδέτες όπως αυξητικούς παράγοντες (π.χ. EGF, ινσουλίνη)

Έχουν εγγενή ενζυματική δράση: φωσφορυλιώνουν τα υπολείμματα τυροσίνης στον εαυτό τους και σε άλλες πρωτεΐνες

Πώς λειτουργούν τα RTK;

Ένας συνδέτης συνδέεται με την εξωκυτταρική περιοχή του RTK.

Αυτό προκαλεί διμερισμό (δύο RTK ζευγαρώνουν).

Οι ενδοκυτταρικές περιοχές κινάσης αυτοφωσφορυλιώνονται μεταξύ τους σε υπολείμματα τυροσίνης.

Αυτές οι φωσφοτυροσίνες δρουν ως θέσεις σύνδεσης για τις πρωτεΐνες σηματοδότησης.

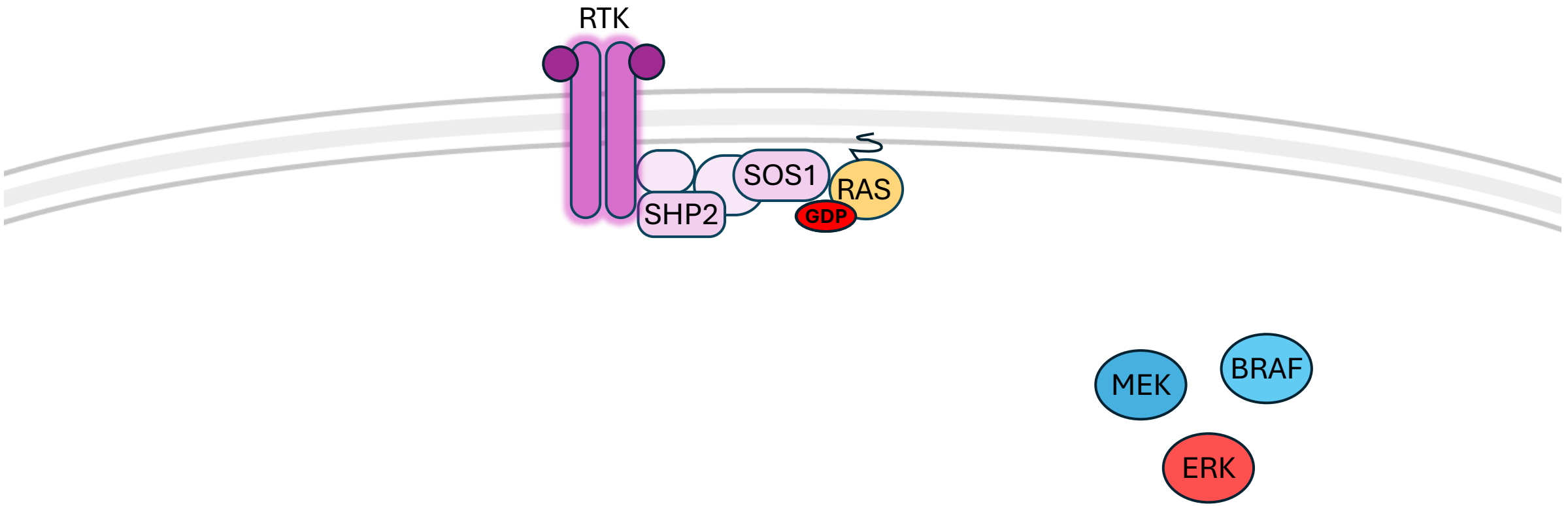
Γιατί είναι σημαντικά τα RTK;

Ρυθμίζουν τον πολλαπλασιασμό, τη διαφοροποίηση, το μεταβολισμό και την επιβίωση των κυττάρων.

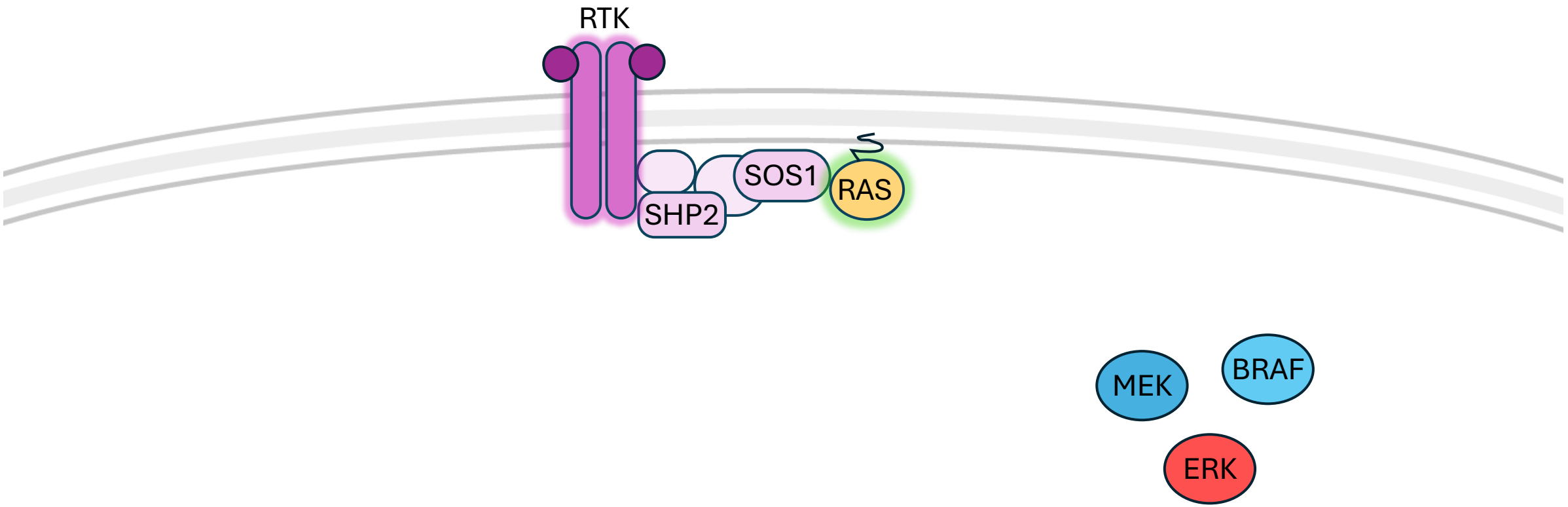
Οι μεταλλάξεις ή η υπερενεργοποίηση των RTKs συνδέονται με καρκίνο και άλλες ασθένειες.

Τα RTK είναι στόχοι για θεραπείες καρκίνου, όπως οι αναστολείς κινάσης τυροσίνης (π.χ. imatinib, erlotinib).

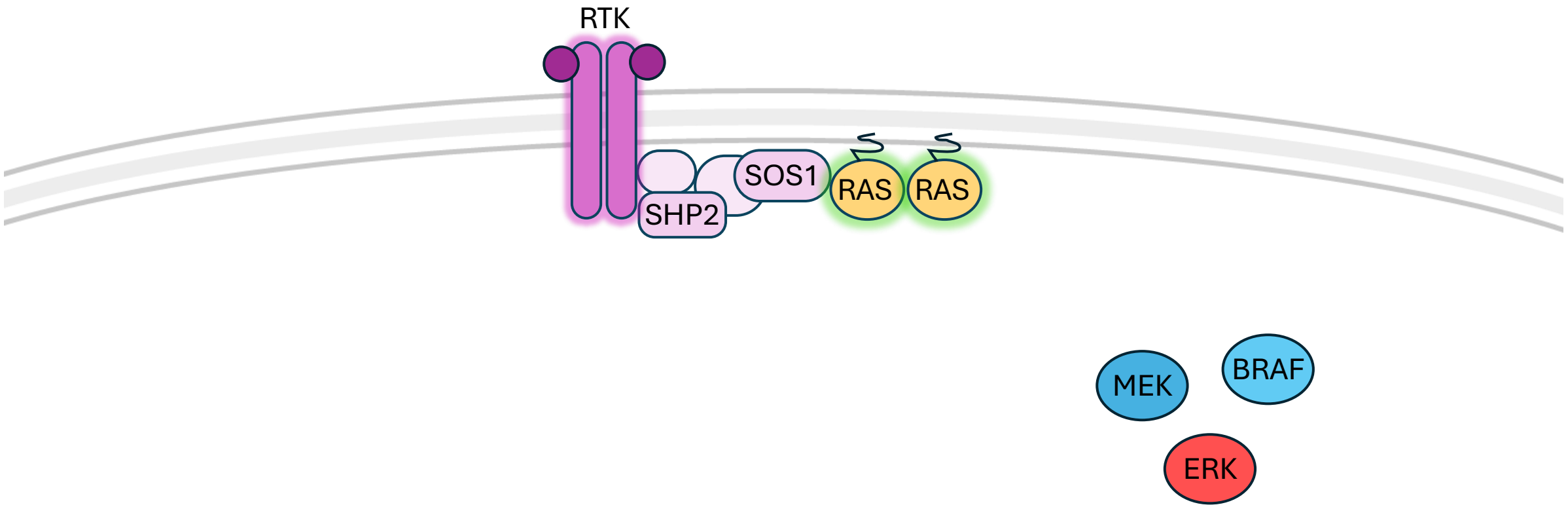
The RTK/MAPK/ERK signaling pathway



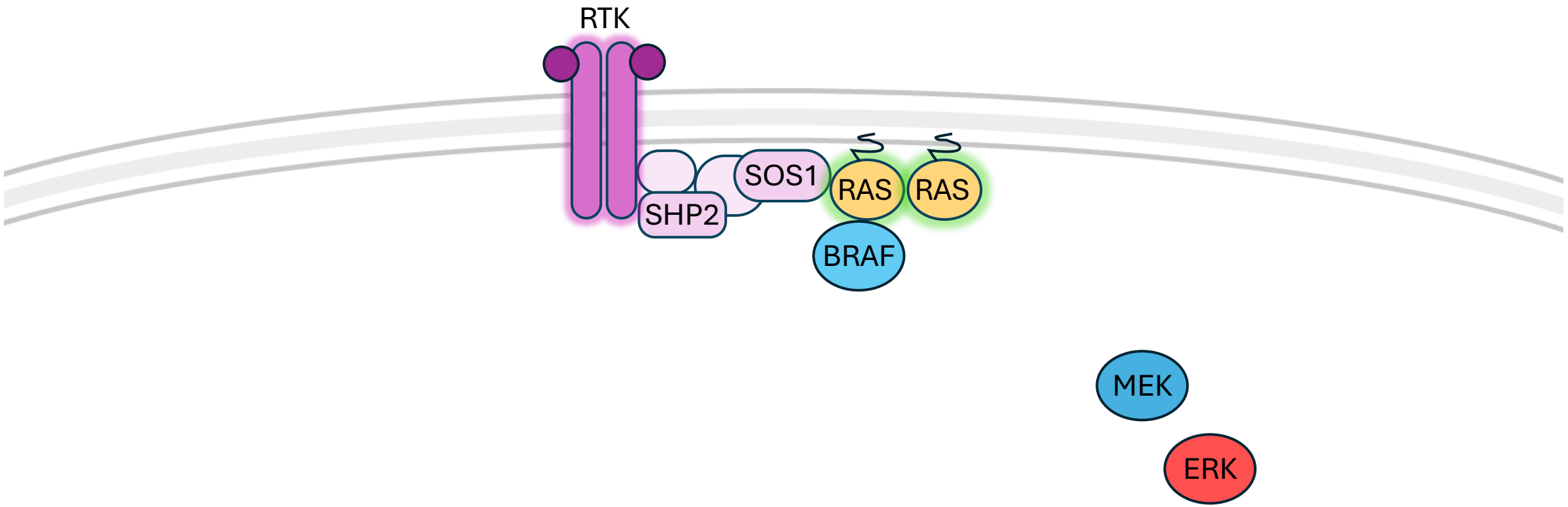
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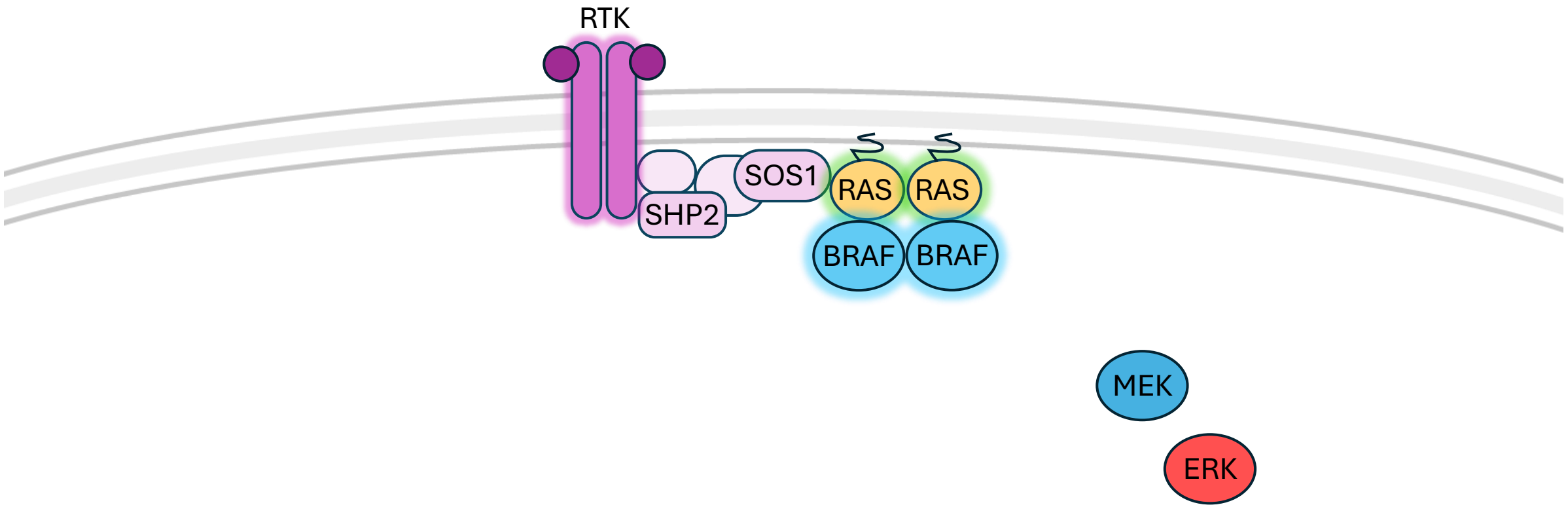
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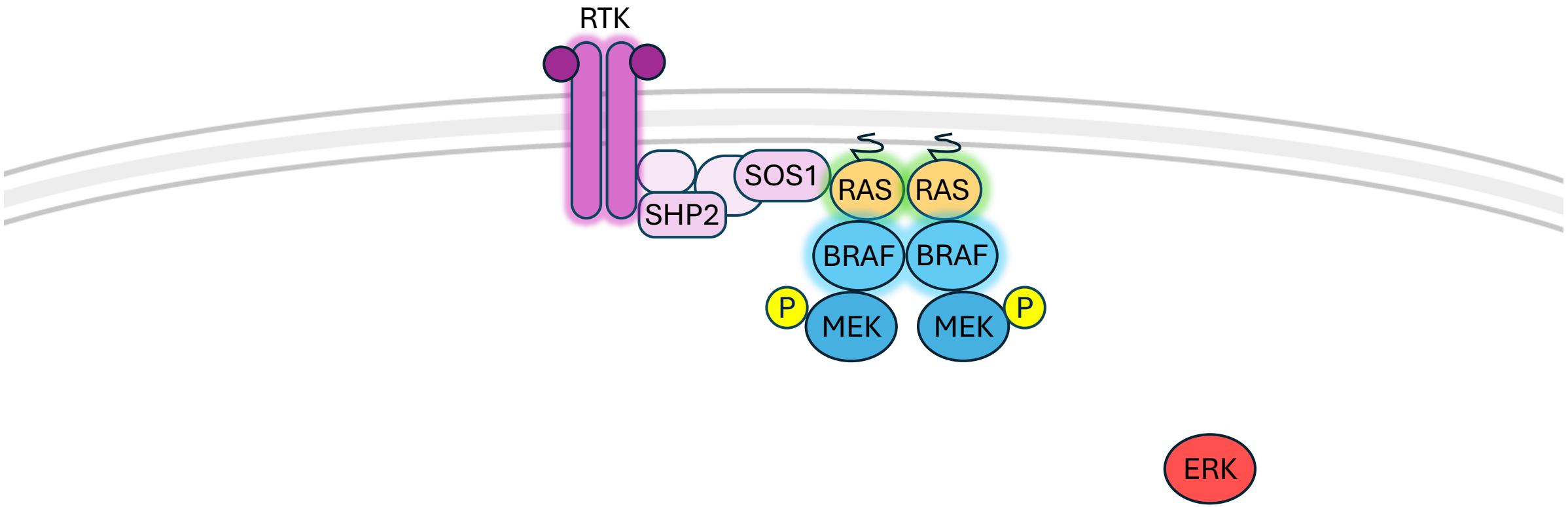
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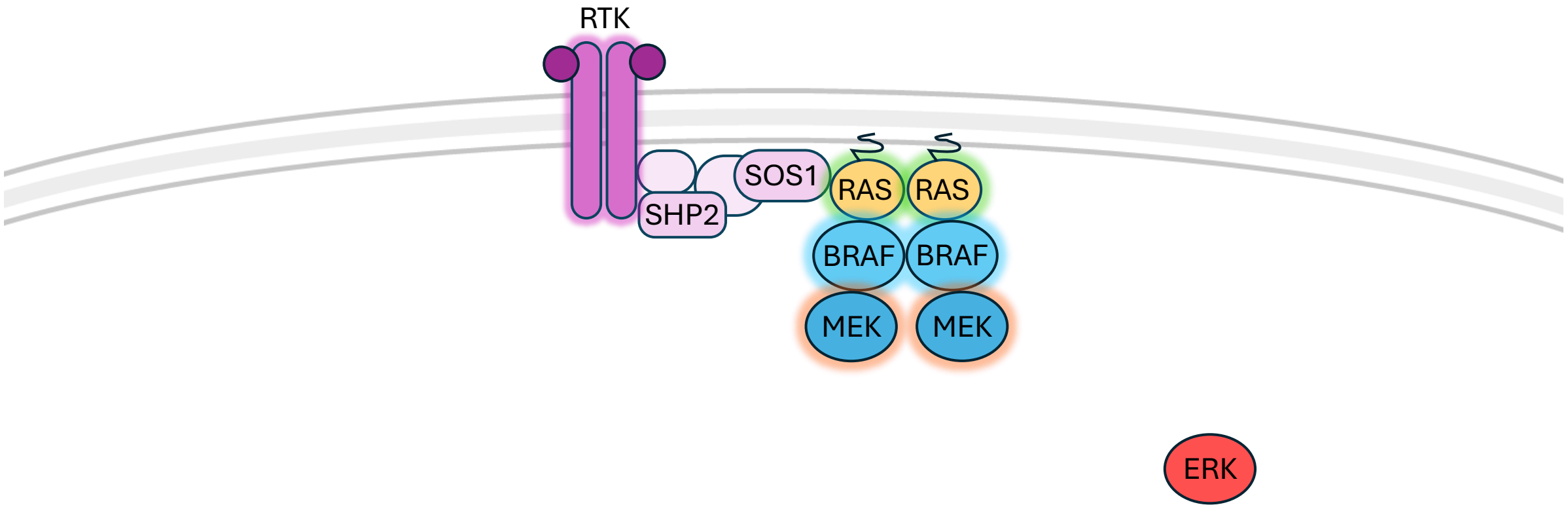
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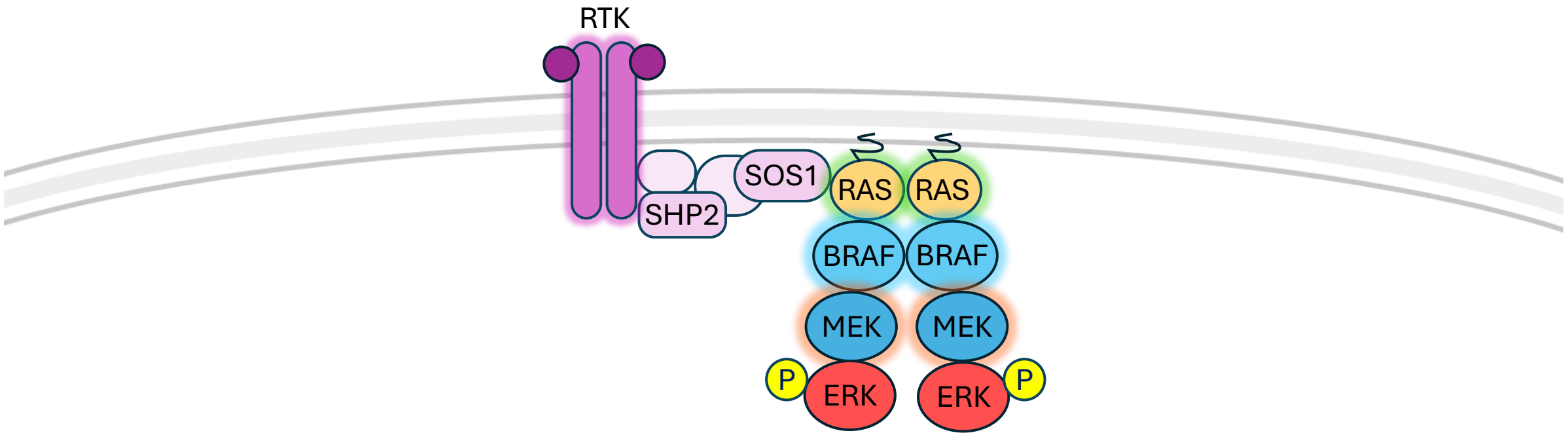
Oncogenic alterations



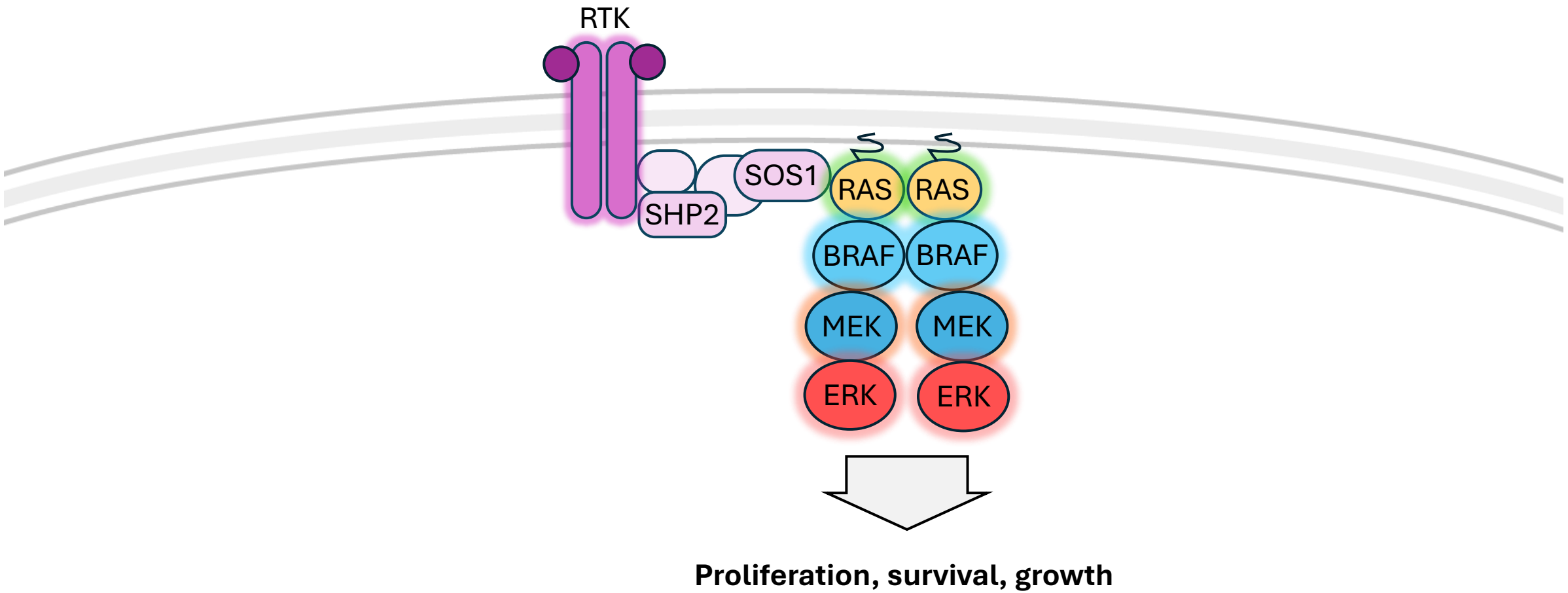
The RTK/MAPK/ERK signaling pathway



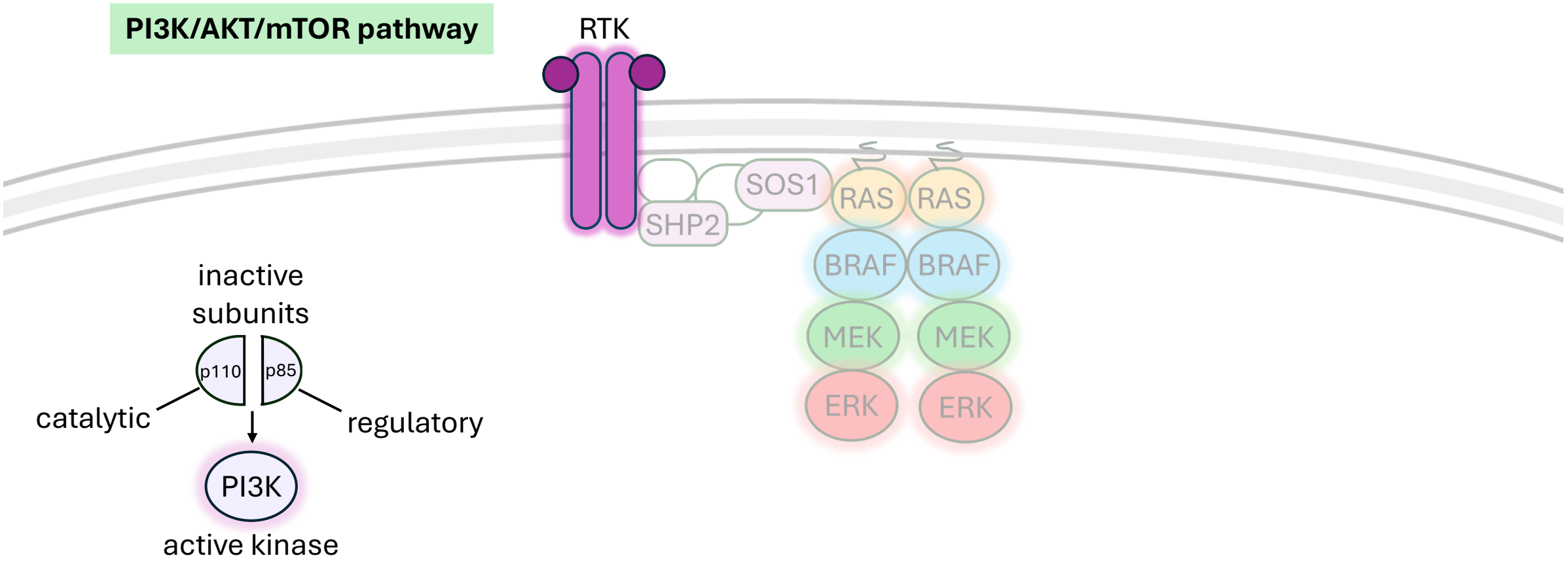
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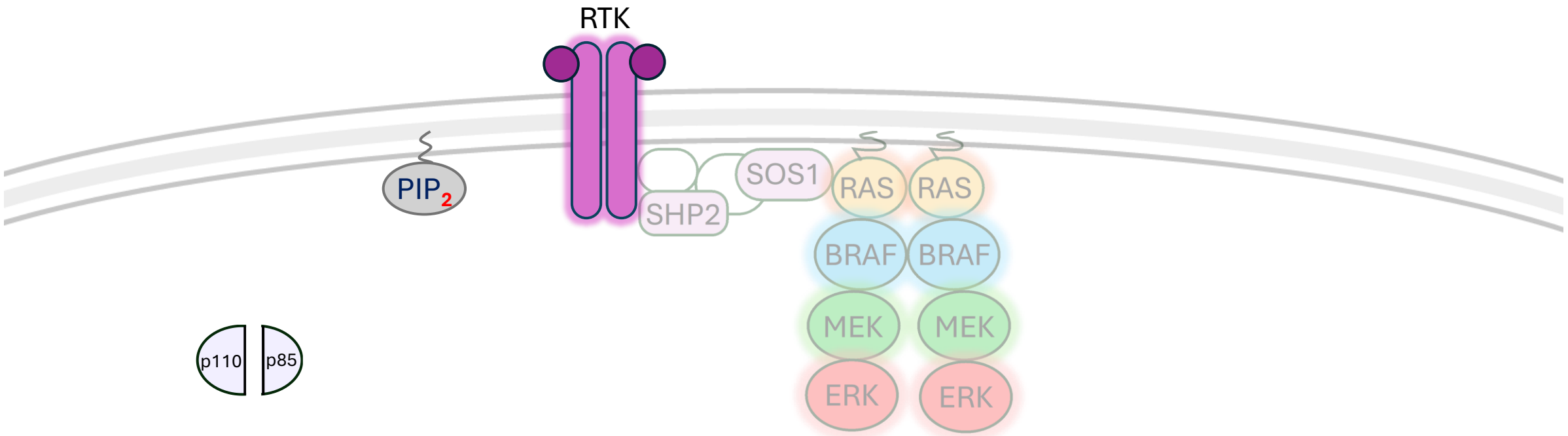
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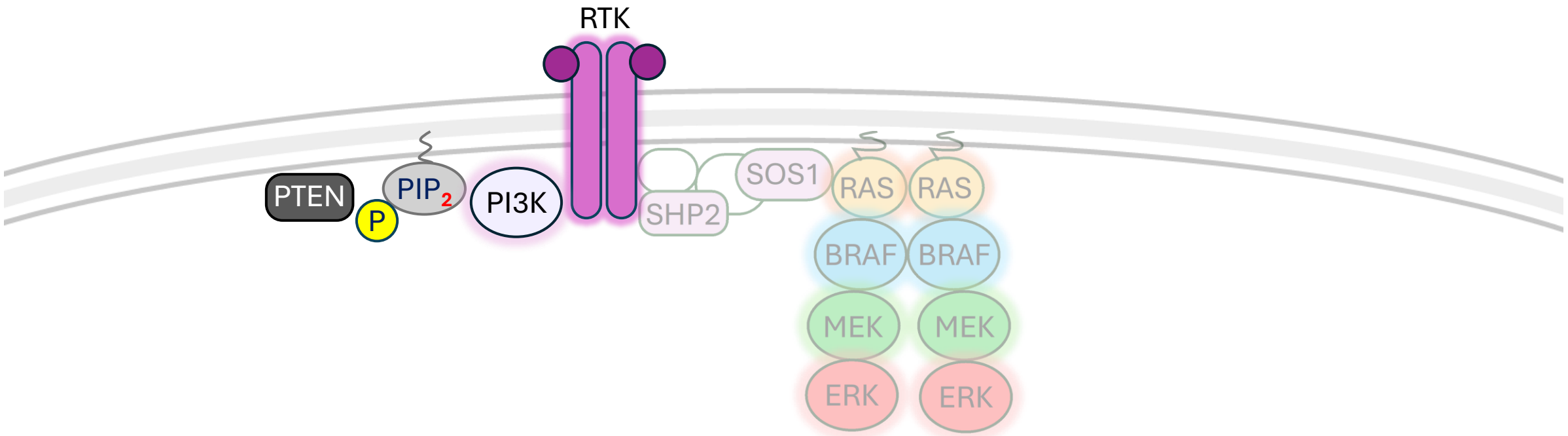
The PI3K/AKT/mTOR signaling pathway



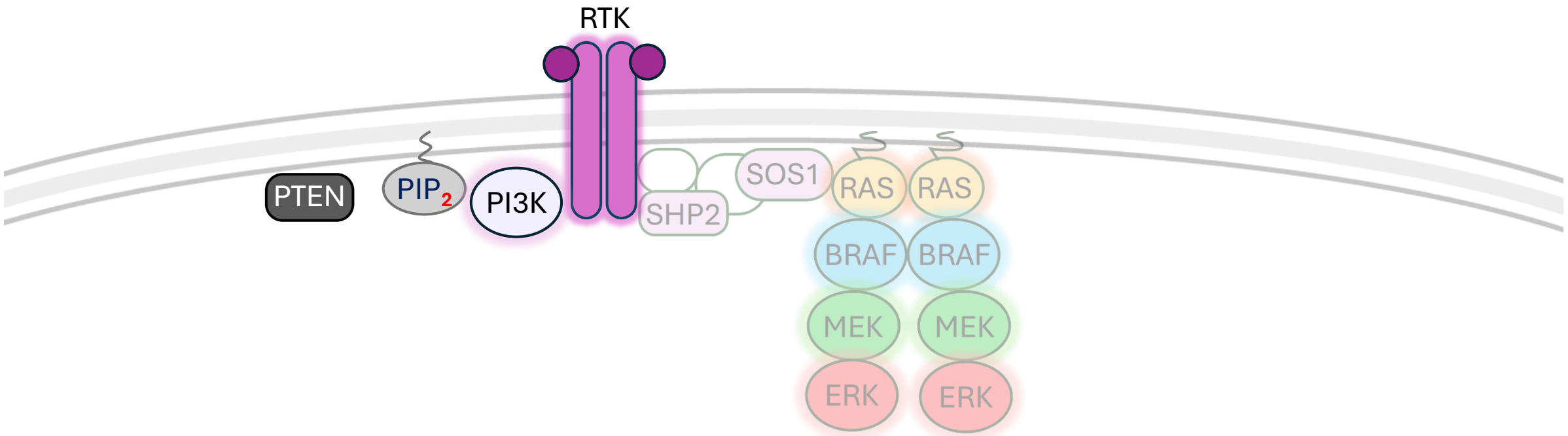
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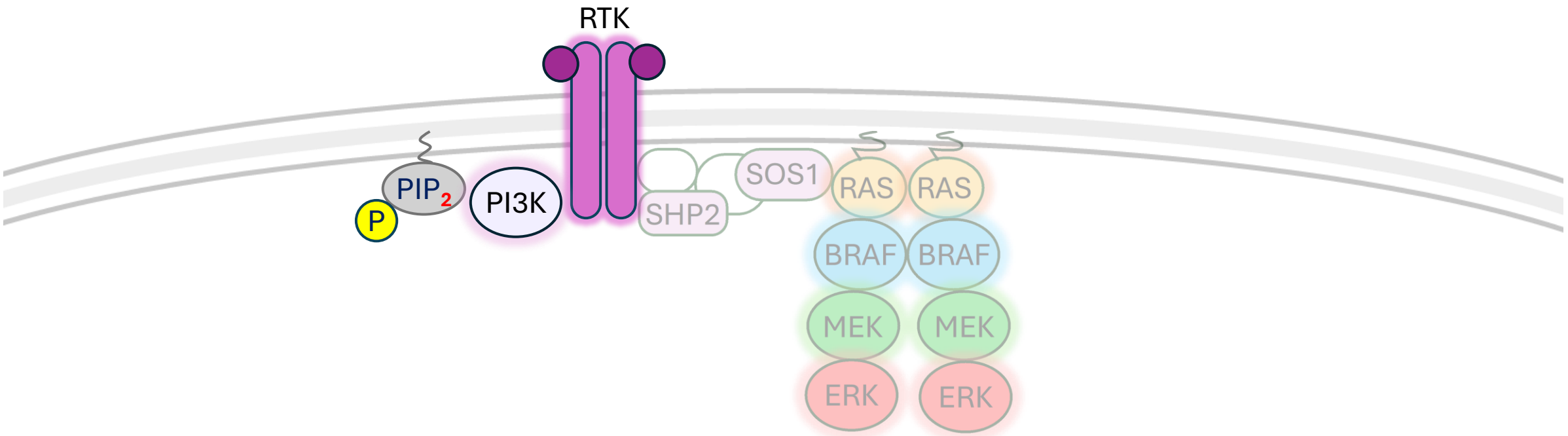
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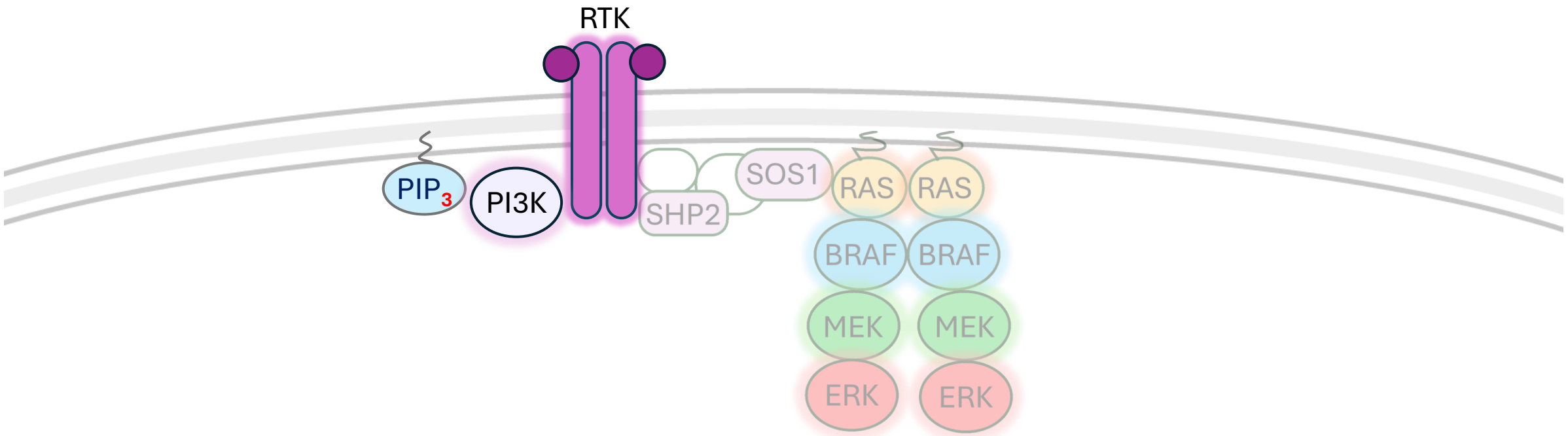
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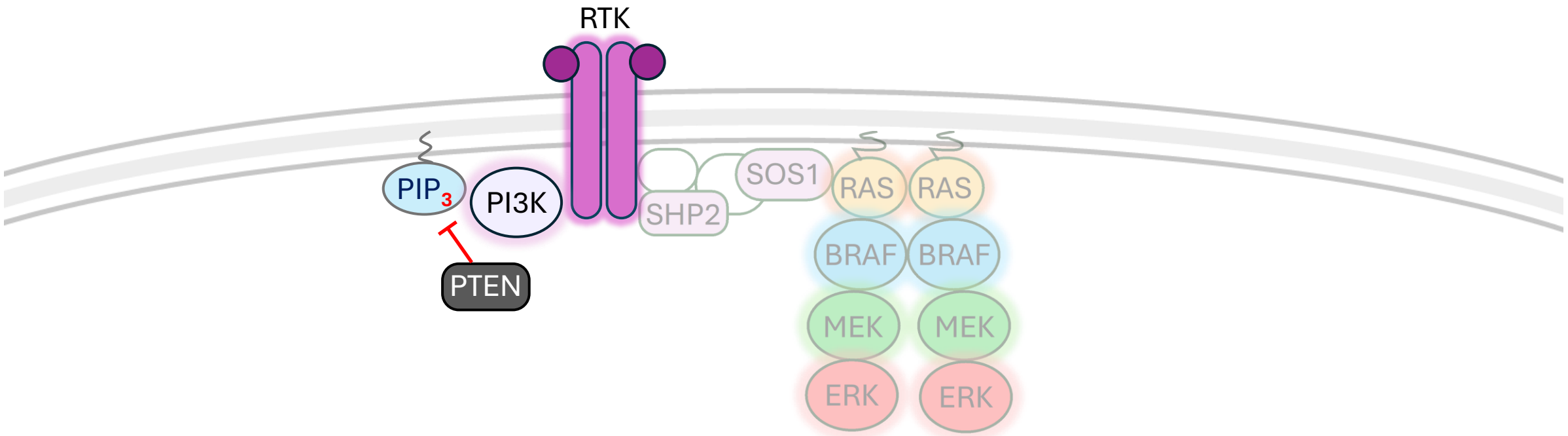
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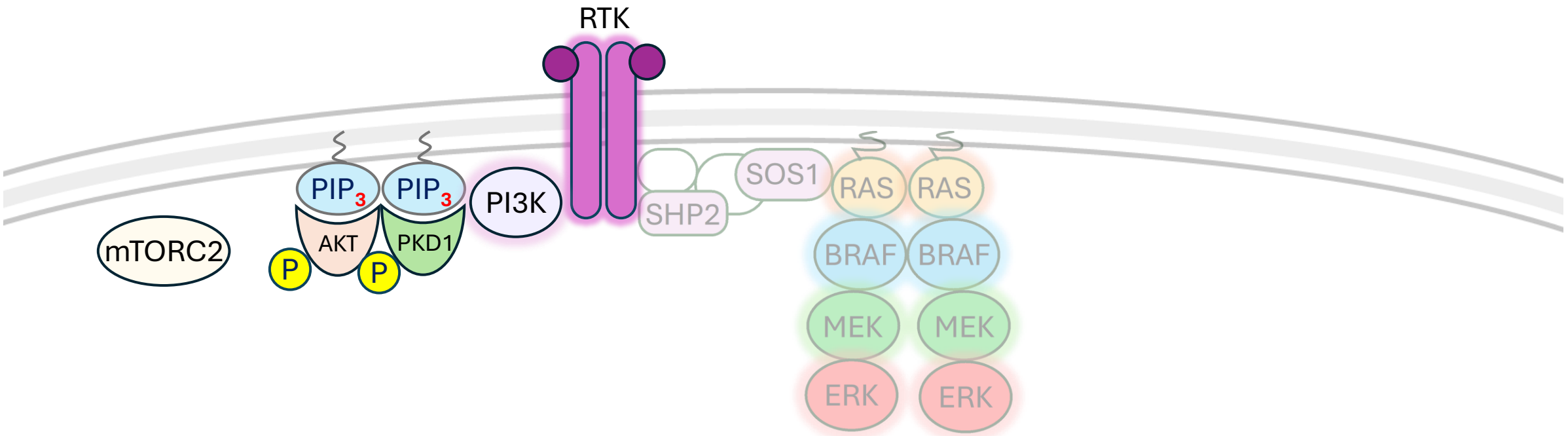
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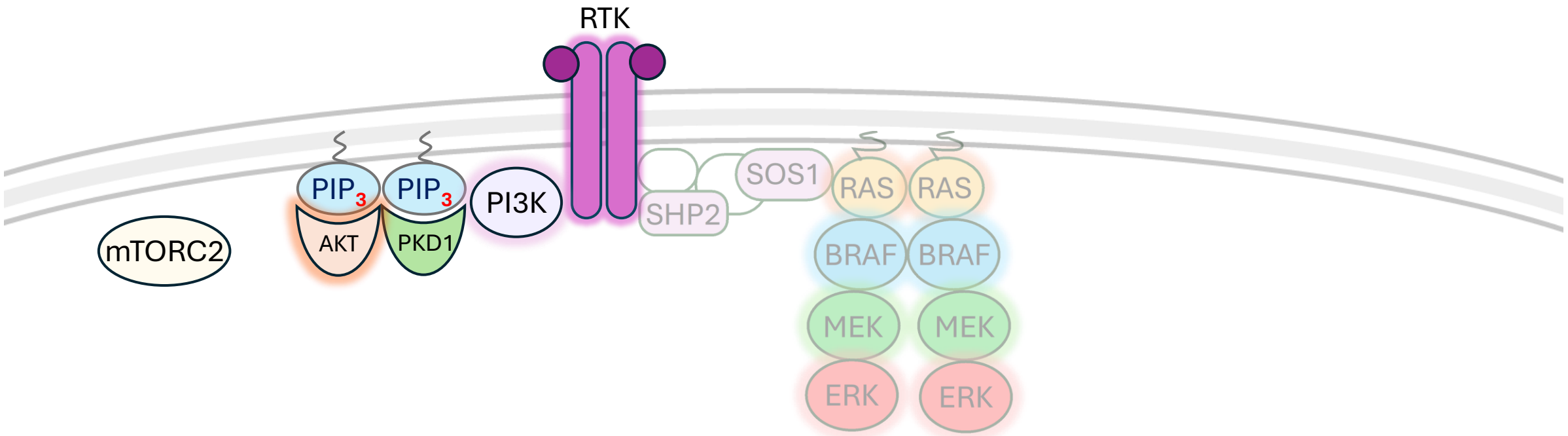
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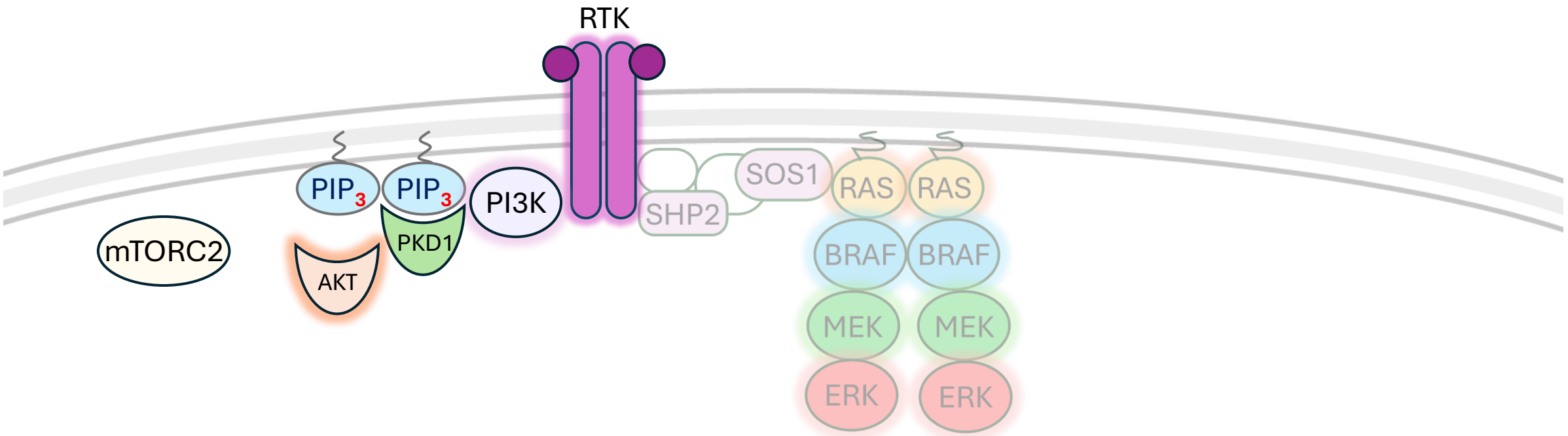
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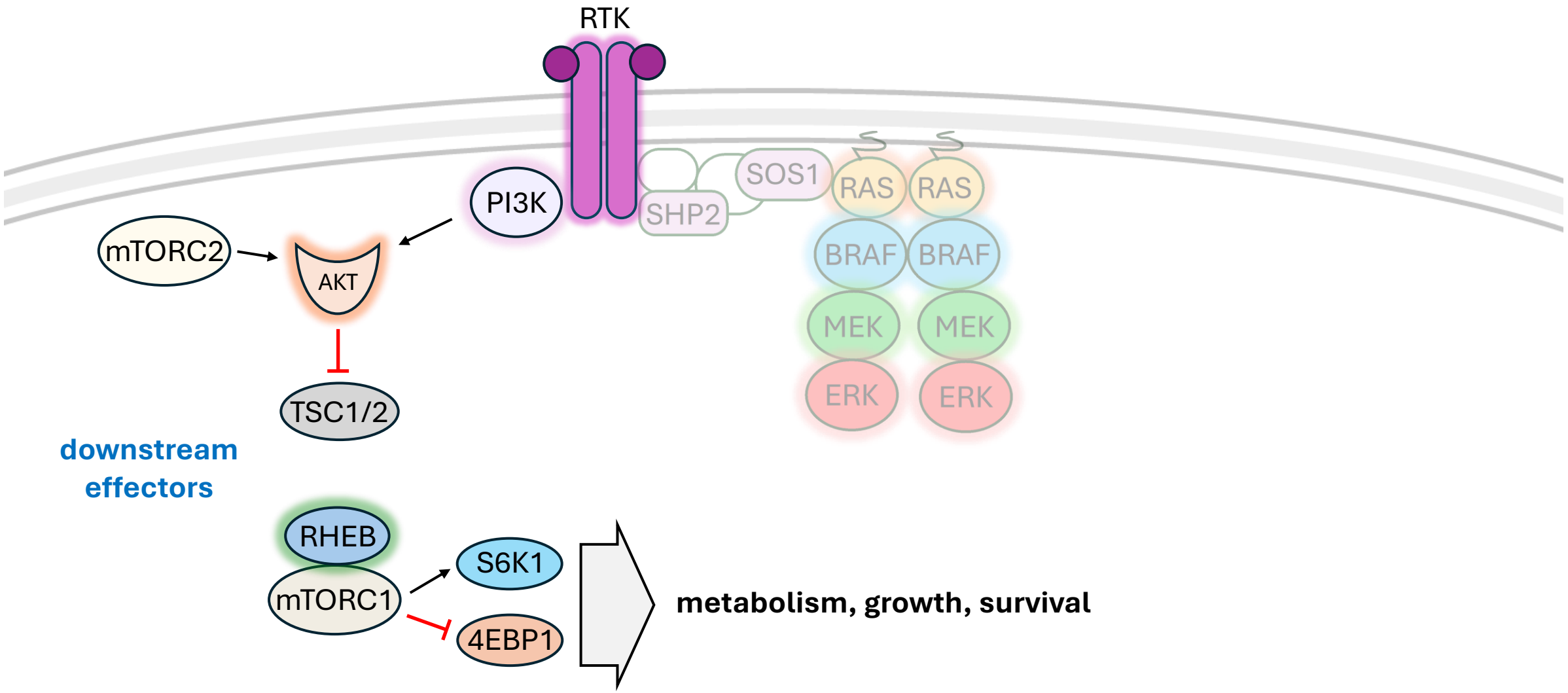
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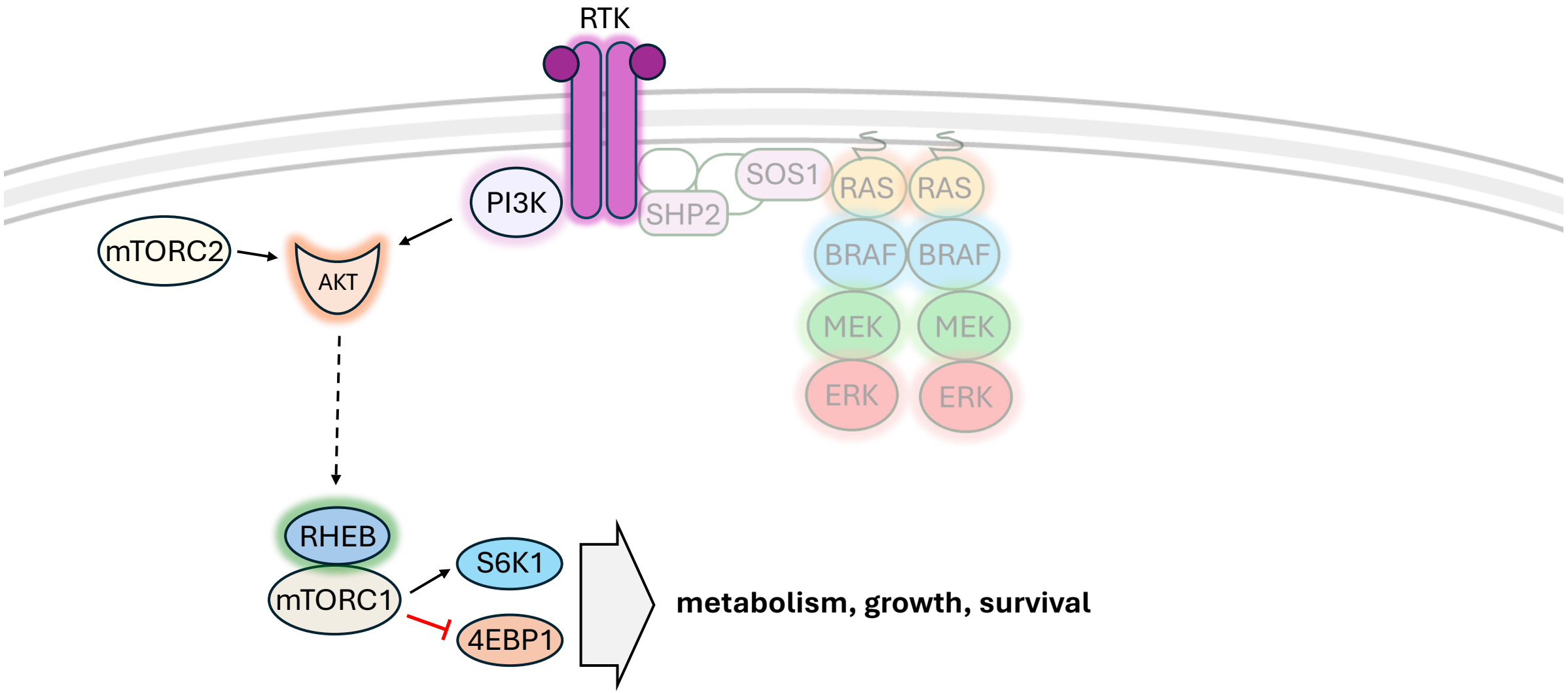
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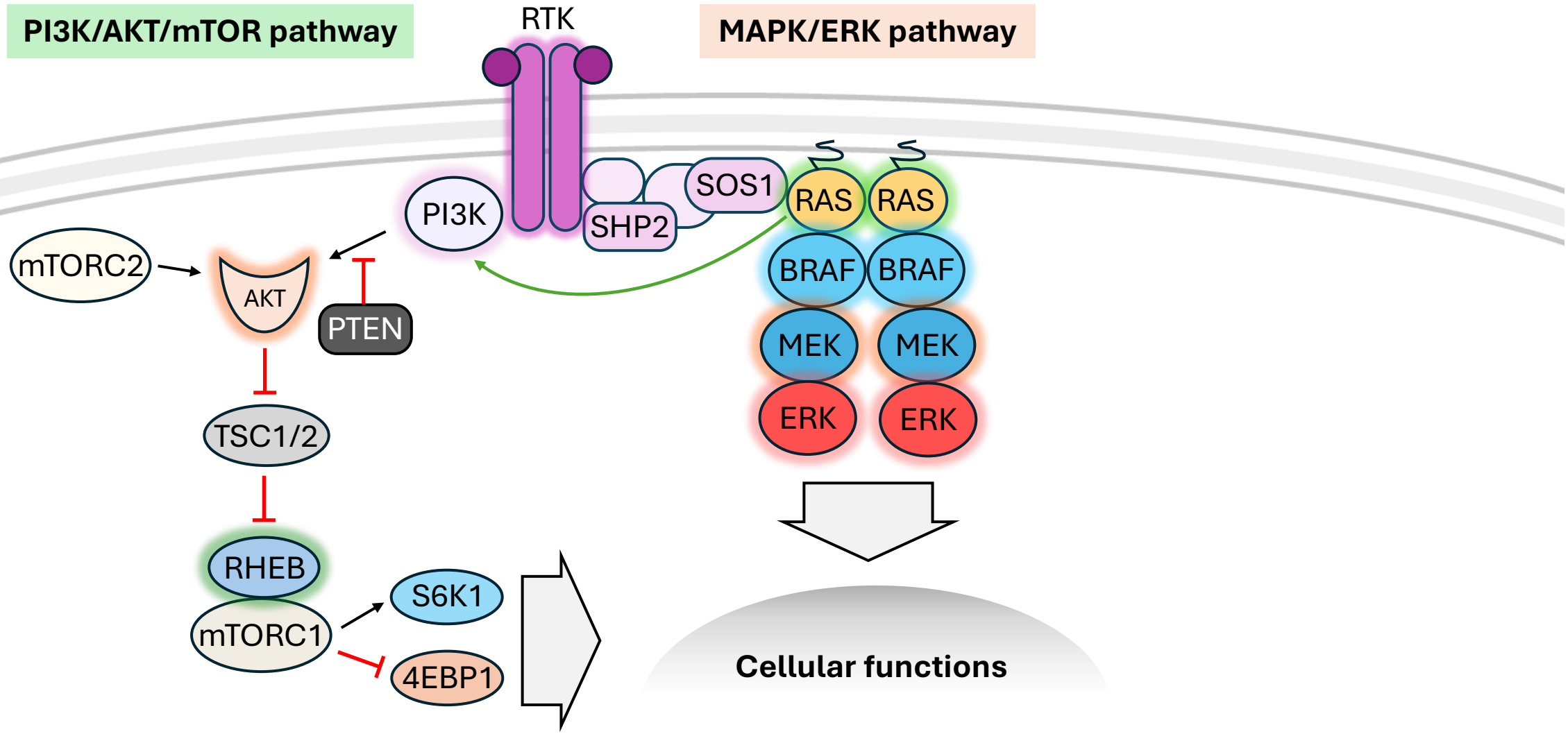
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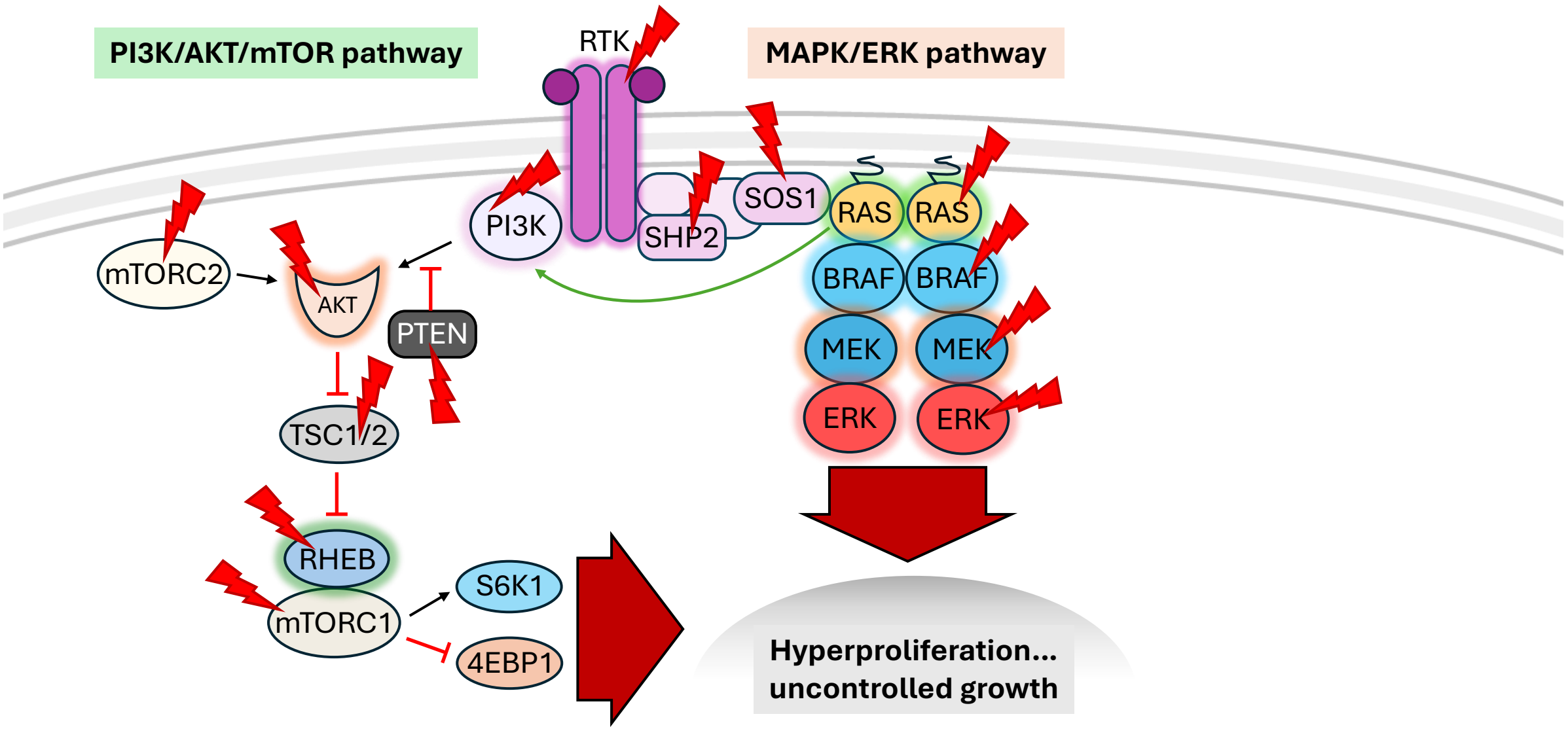
The PI3K/AKT/mTOR signaling pathway



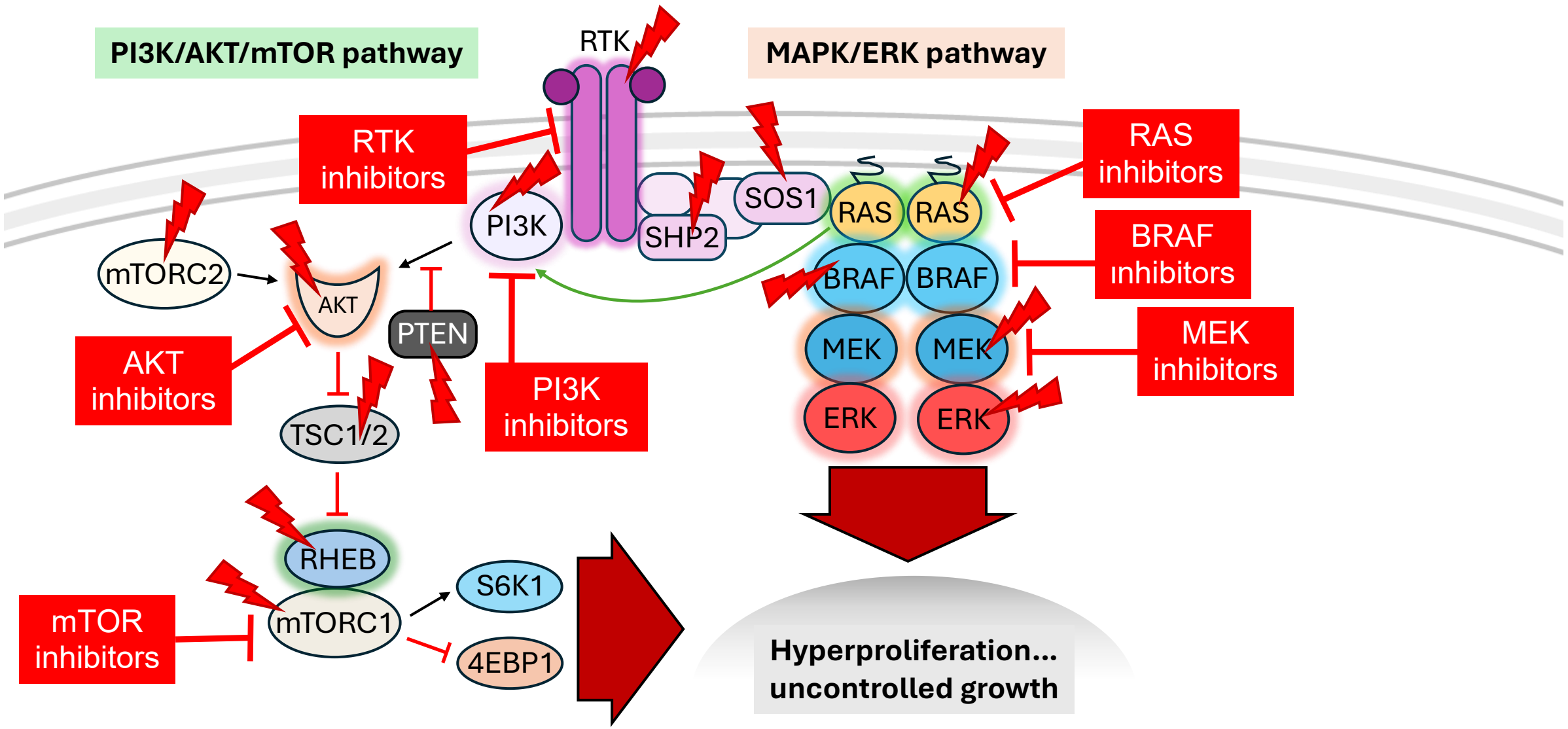
Overview of MAPK/ERK & PI3K/AKT/mTOR pathways

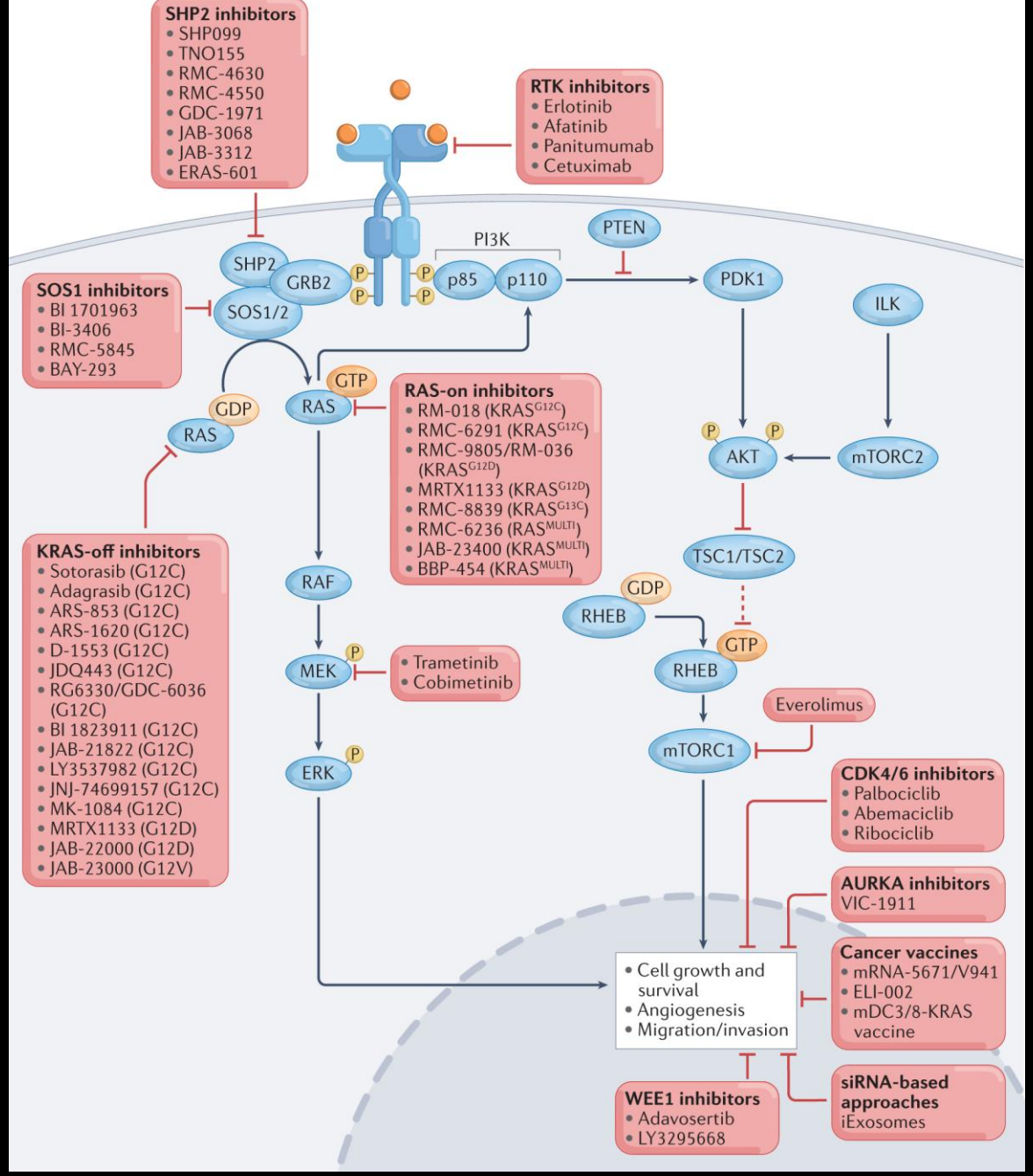


Deregulation of MAPK/ERK & PI3K/AKT/mTOR pathways

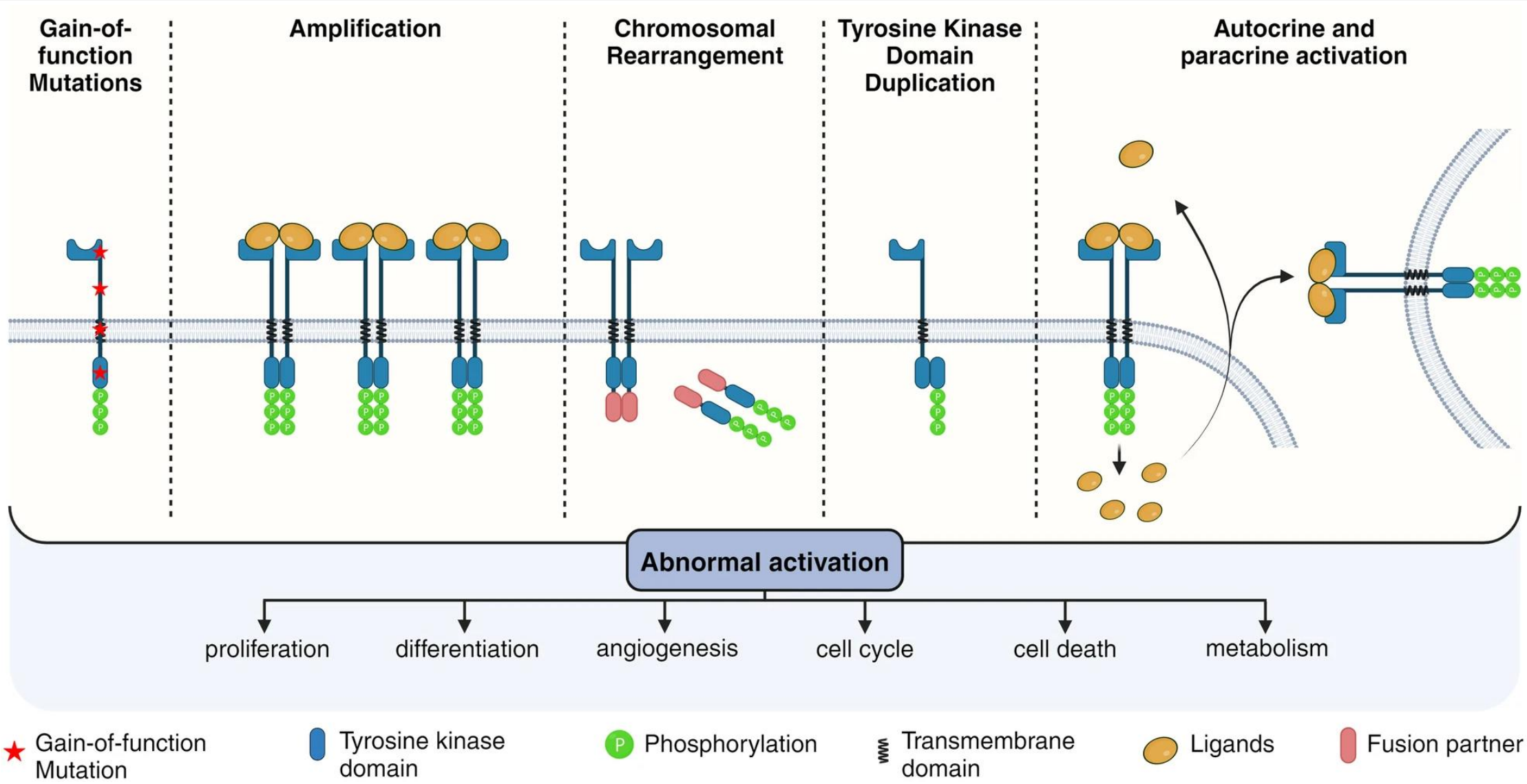


Targeting the MAPK/ERK & PI3K/AKT/mTOR pathways




SHP2 inhibitors
• SHP099
• TNO155
• RMC-4630
• RMC-4550
• GDC-1971
• JAB-3068
• JAB-3312
• ERAS-601
RTK inhibitors
• Erlotinib
• Afatinib
• Panitumumab
• Cetuximab
PI3K
PTEN
SHP2
GRB2
SOS1/2
p85
p110
PDK1
ILK
SOS1 inhibitors
• BI 1701963
• BI-3406
• RMC-5845
• BAY-293
GTP
GDP
RAS
RAS-on inhibitors
• RM-018 (KRASG12C)
• RMC-6291 (KRASG12C)
• RMC-9805/RM-036 (KRASG12D)
• MRTX1133 (KRASG12D)
• RMC-8839 (KRASG13C)
• RMC-6236 (RASMULTI)
• JAB-23400 (KRASMULTI)
• BBP-454 (KRASMULTI)
AKT
mTORC2
TSC1/TSC2
RAF
GDP
RHEB
GTP
RHEB
MEK
• Trametinib
• Cobimetinib
Everolimus
mTORC1
ERK
KRAS-off inhibitors
• Sotorasib (G12C)
• Adagrasib (G12C)
• ARS-853 (G12C)
• ARS-1620 (G12C)
• D-1553 (G12C)
• JDQ443 (G12C)
• RG6330/GDC-6036 (G12C)
• BI 1823911 (G12C)
• JAB-21822 (G12C)
• LY3537982 (G12C)
• JNJ-74699157 (G12C)
• MK-1084 (G12C)
• MRTX1133 (G12D)
• JAB-22000 (G12D)
• JAB-23000 (G12V)
CDK4/6 inhibitors
• Palbociclib
• Abemaciclib
• Ribociclib
AURKA inhibitors
VIC-1911
Cancer vaccines
• mRNA-5671/V941
• ELI-002
• mDC3/8-KRAS vaccine
• Cell growth and survival
• Angiogenesis
• Migration/invasion
siRNA-based approaches
iExosomes
WEE1 inhibitors
• Adavosertib
• LY3295668

RTKs dysregulation mechanisms



https://www.nature.com/articles/s41392-024-01899-w

KRAS – Mechanism of Gain-of-Function

KRAS is a small GTPase that normally cycles between active (GTP-bound) and inactive (GDP-bound) states.

Mutations like **G12D, G12V, G13D** impair its ability to hydrolyze GTP.

As a result, KRAS remains **locked in its active form**, continuously stimulating downstream effectors like RAF → MEK → ERK.

This leads to **persistent mitogenic signaling**, promoting proliferation and resistance to apoptosis.

BRAF – Mechanism of Gain-of-Function

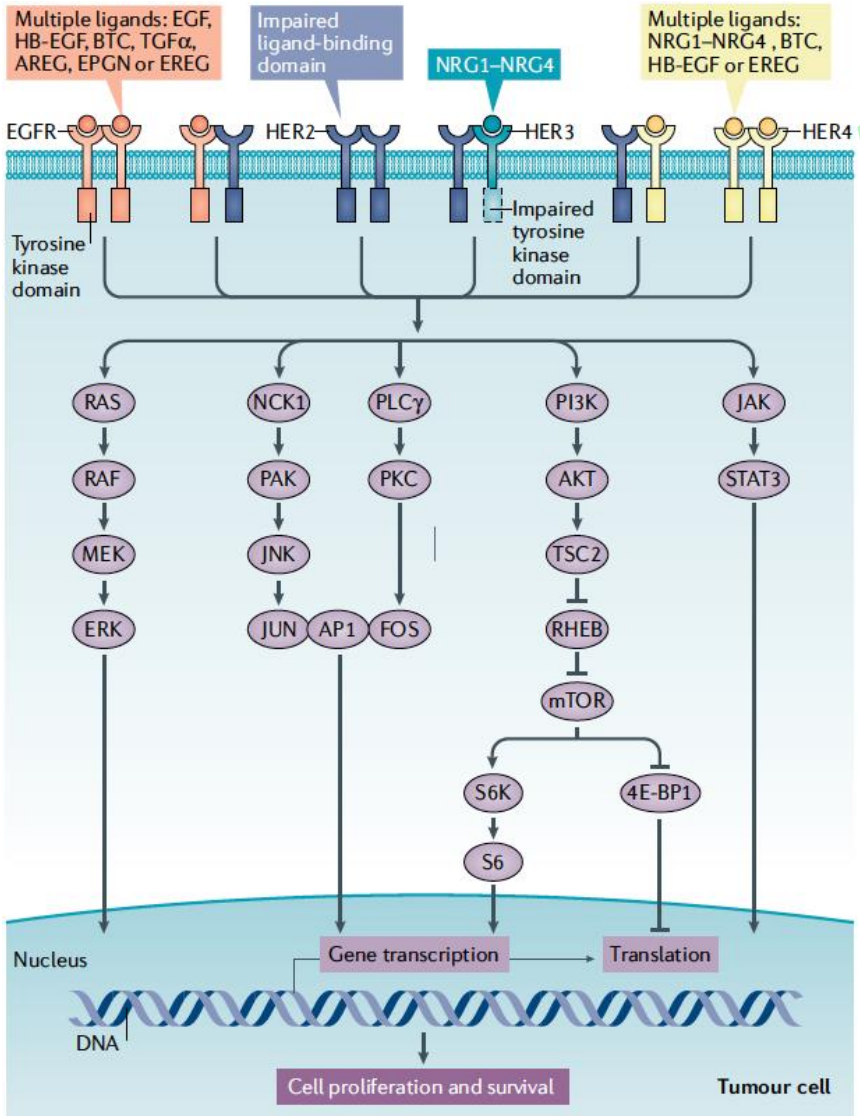
BRAF is a serine/threonine kinase activated by RAS.

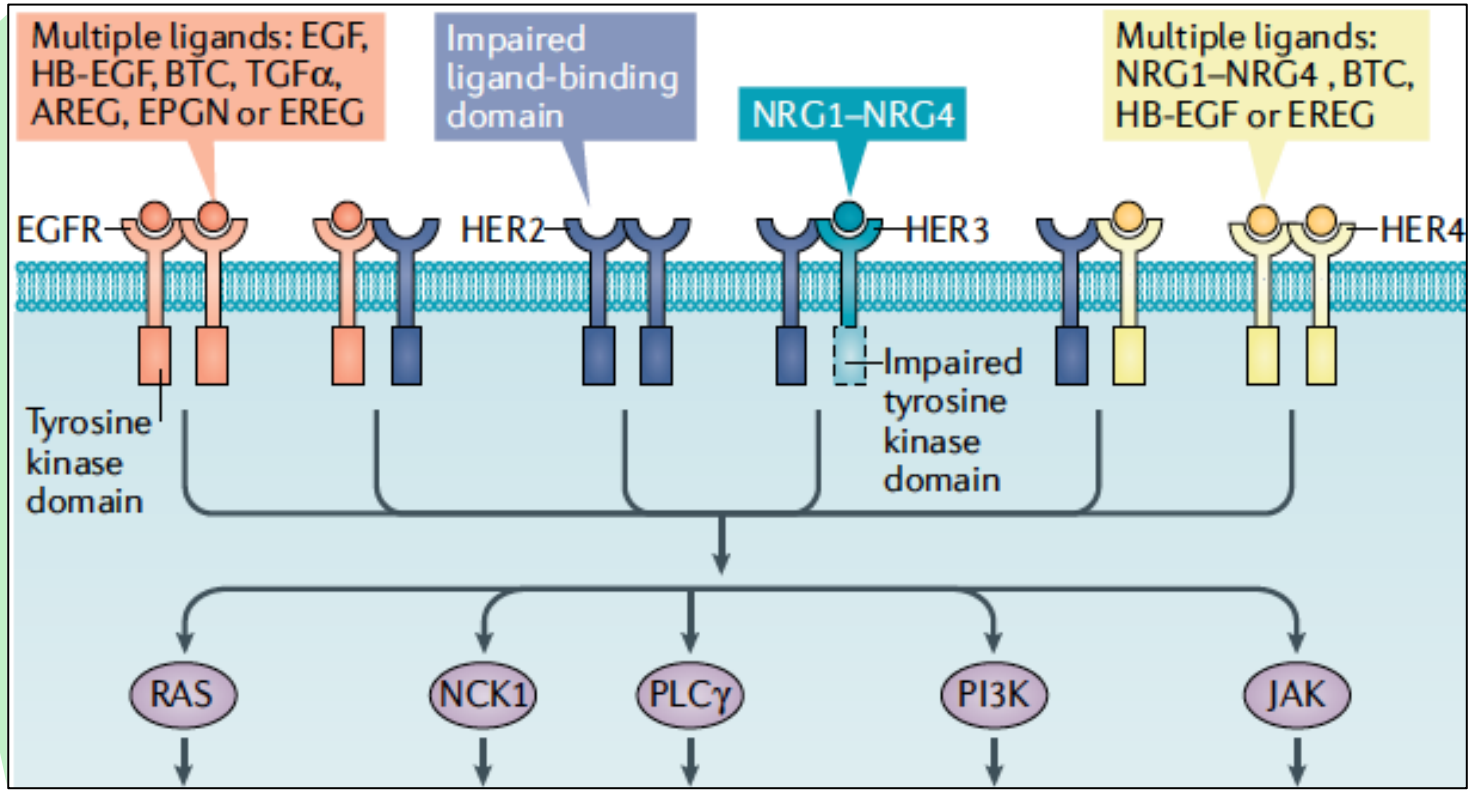
The most common mutation, **V600E**, substitutes valine with glutamic acid at position 600.

This mimics phosphorylation and renders BRAF **constitutively active**, even without upstream RAS signals.

The result is **continuous activation of MEK and ERK**, driving oncogenic transformation.

ERBB receptor family signaling

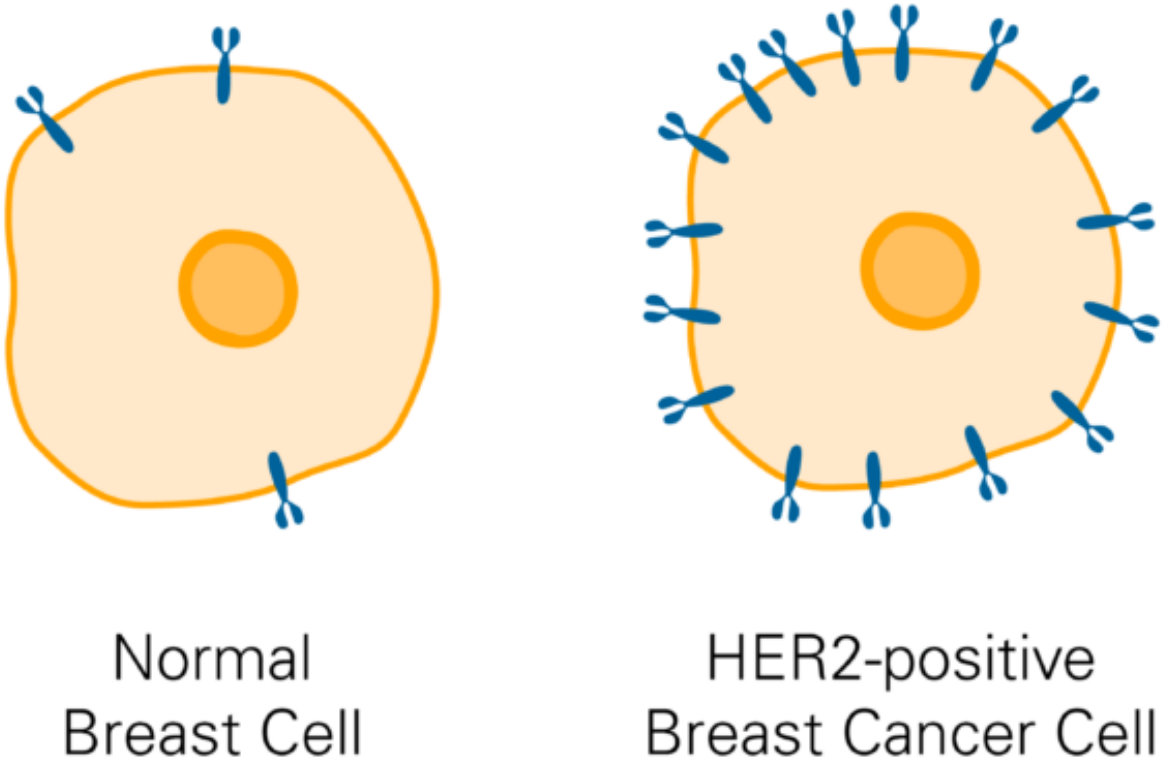




Εάν η περιοχή δέσμευσης συνδέτη είναι εξασθενημένη:
Ο υποδοχέας μπορεί να μην ανταποκρίνεται σε εξωκυτταρικά σήματα.
Μπορεί ακόμα να ενεργοποιηθεί έμμεσα μέσω διμερισμού με άλλους υποδοχείς.
Σε ορισμένες περιπτώσεις, μεταλλάξεις ή υπερέκφραση μπορεί να οδηγήσουν σε ενεργοποίηση ανεξάρτητη από συνδέτη, συμβάλλοντας στην ογκογένεση.

HER2 positive Breast Cancer

About 20% of breast cancer cases are HER2 positive



Normal Breast Cell

HER2-positive Breast Cancer Cell

Bladder cancer, gastrointestinal cancers, ovarian cancer and stomach cancer can also be HER2 positive

FDA-approved drugs

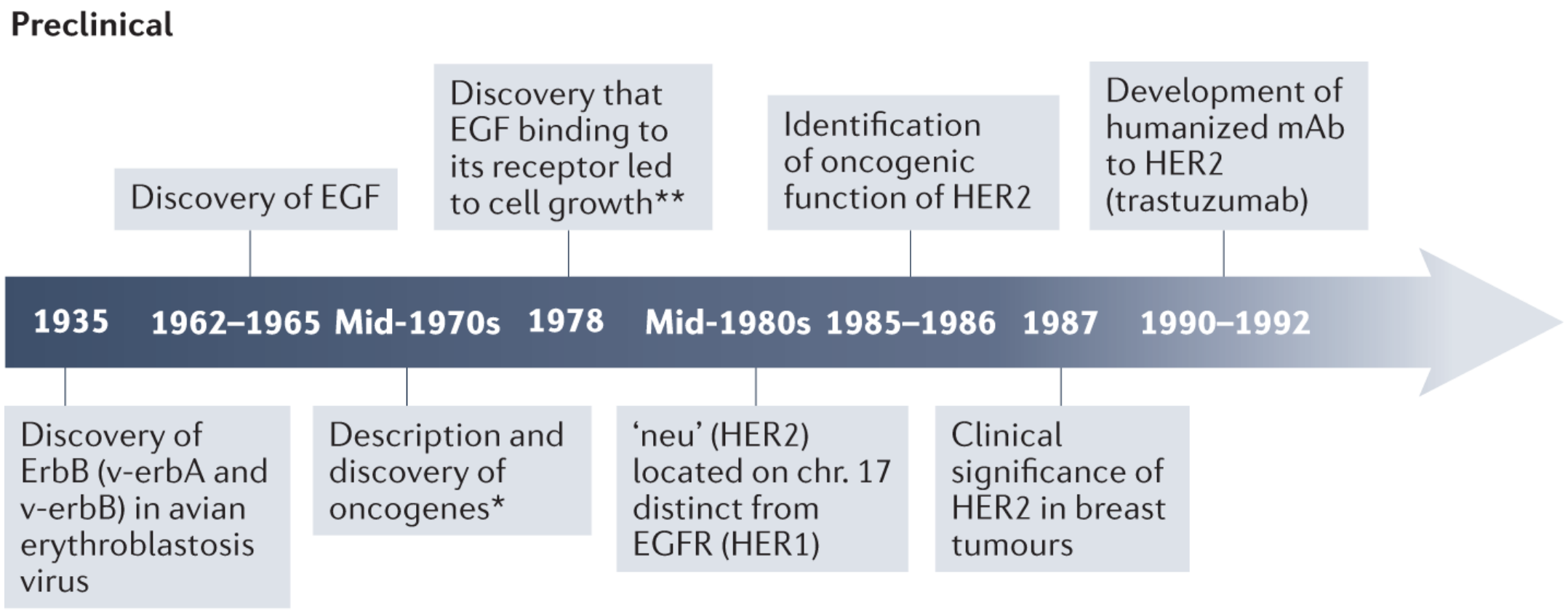
- 3 monoclonal antibodies
- 2 antibody-drug conjugates,
- 3 oral tyrosine kinase inhibitors

blog.dana-farber.org

HER2: human epidermal growth factor receptor 2

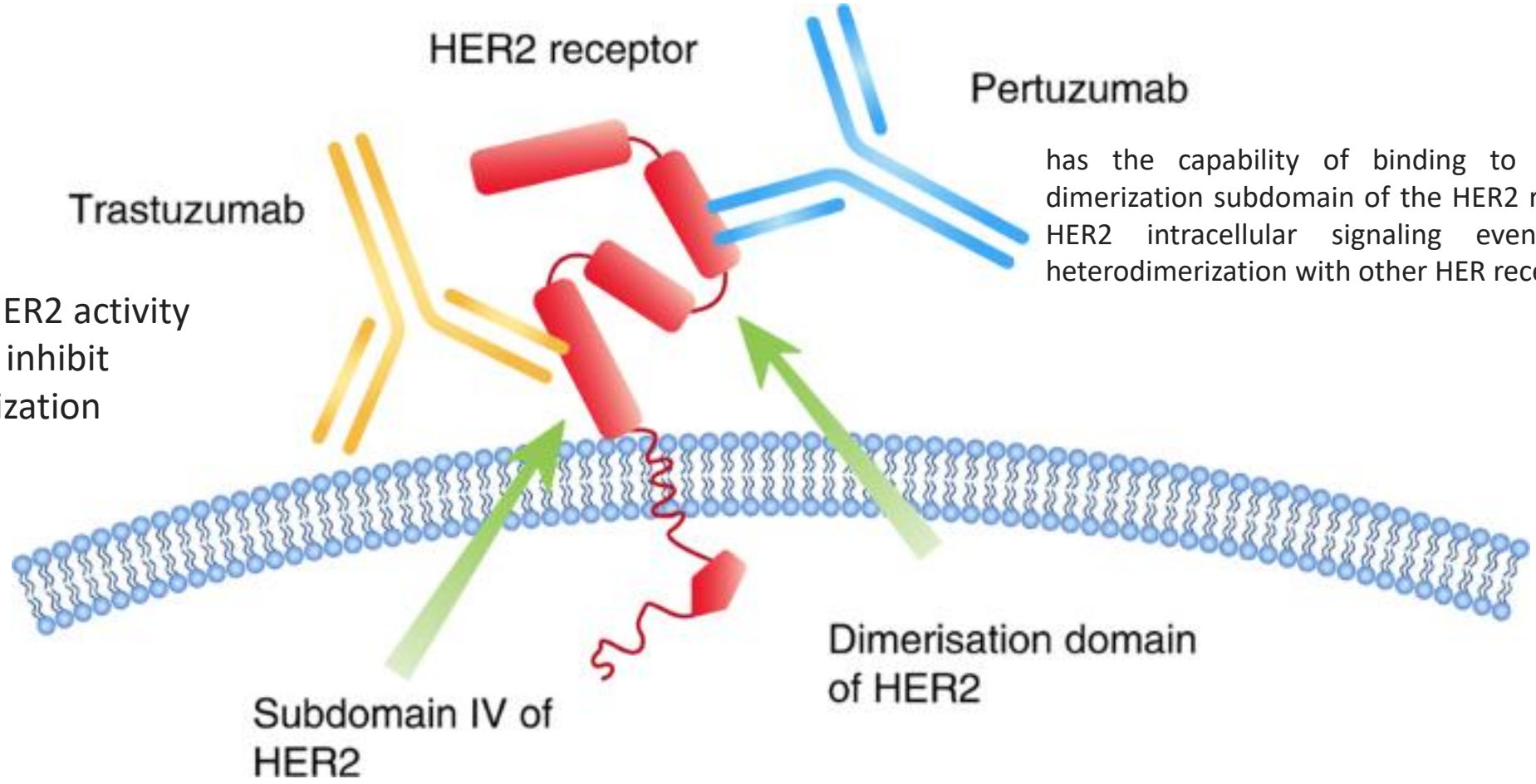
Evolution of HER2 as biomarker & targeted therapy in breast cancer I

Swain, Nat Rev Drug DIscov, 2023, 22, p101–126



Types of Targeted Therapies: mAb

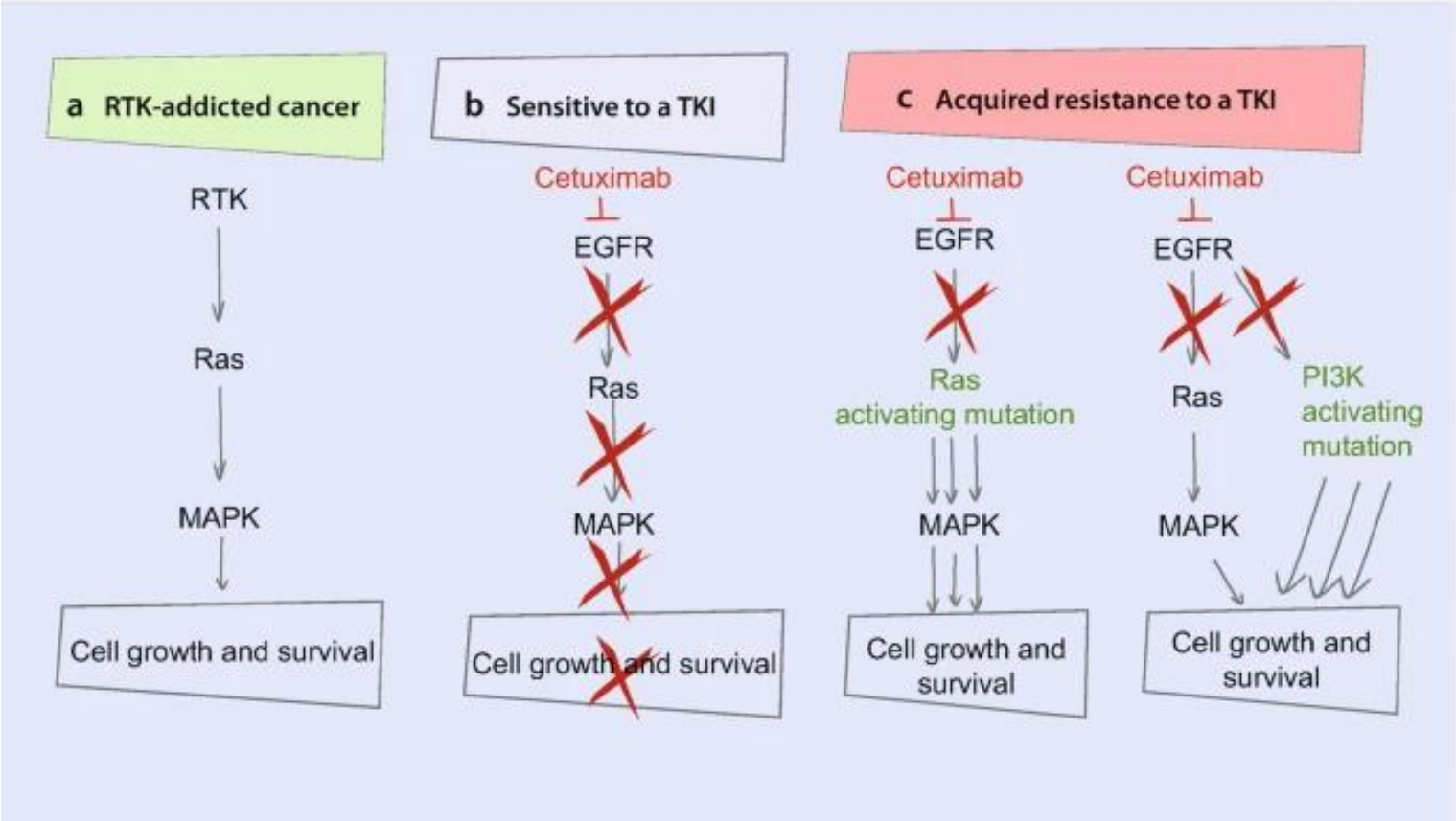
mAb: monoclonal antibodies



suppresses HER2 activity but does not inhibit heterodimerization

has the capability of binding to the extracellular dimerization subdomain of the HER2 receptor, reducing HER2 intracellular signaling events by blocking heterodimerization with other HER receptors

Why Do Cancer Cells Develop Resistance to Targeted Therapies?



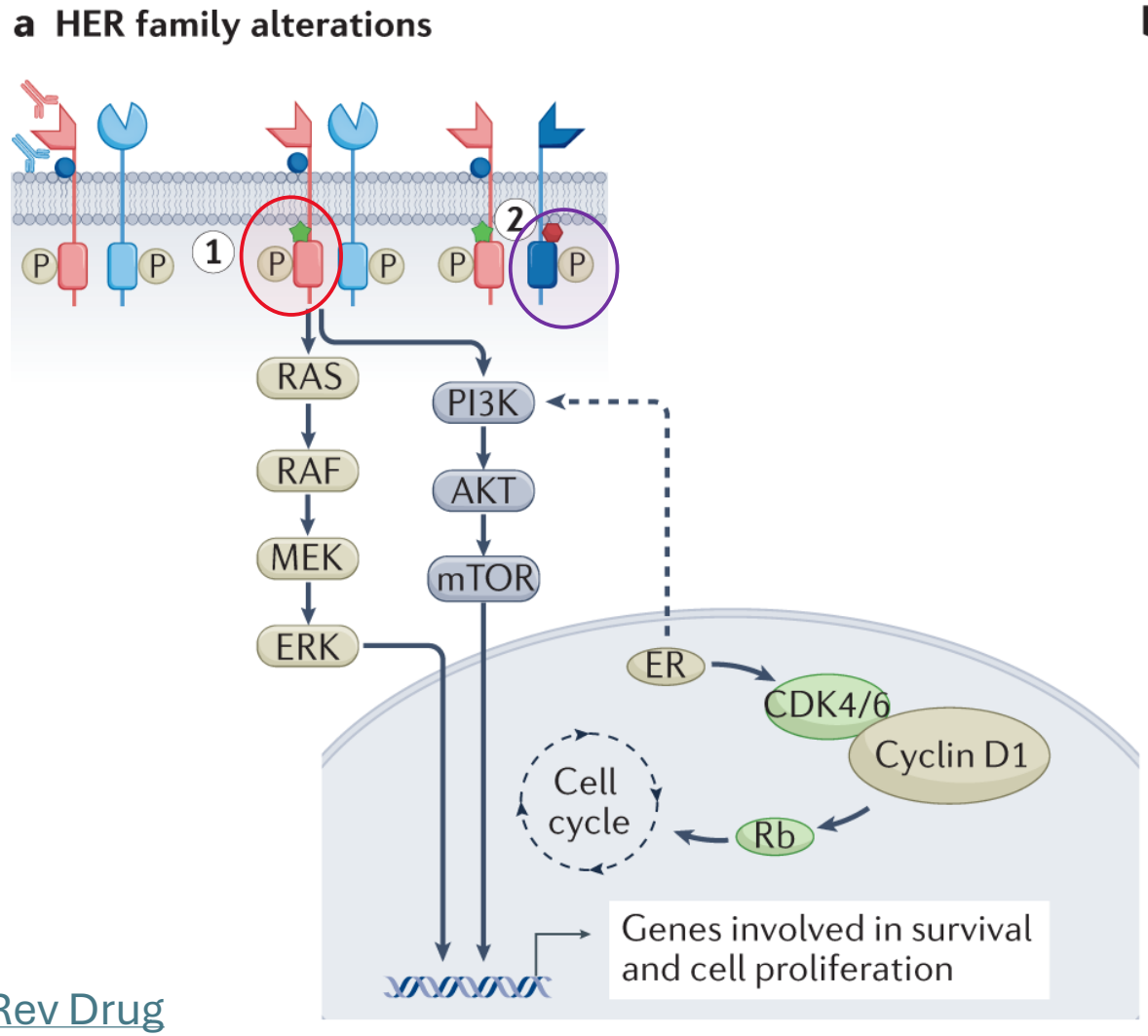
Mutational Activation of an Element in the Pathway Downstream from the Target

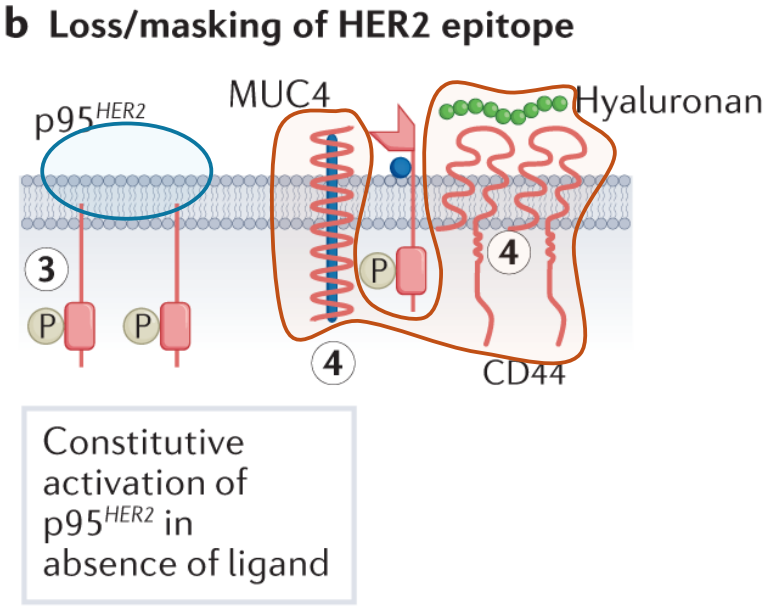
Release from a Negative Feedback Loop

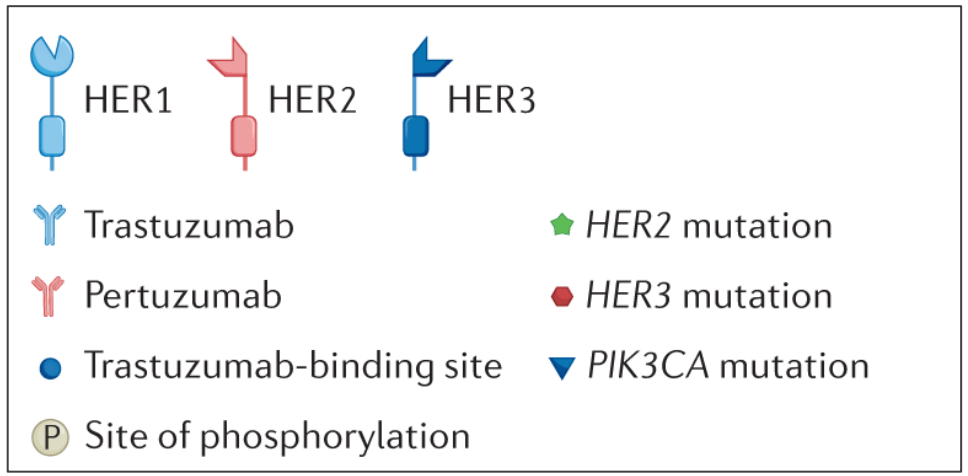
Mutations and Amplifications in the Target

Other Mechanisms of Resistance

Mechanisms of HER2-targeted resistance (a-b)

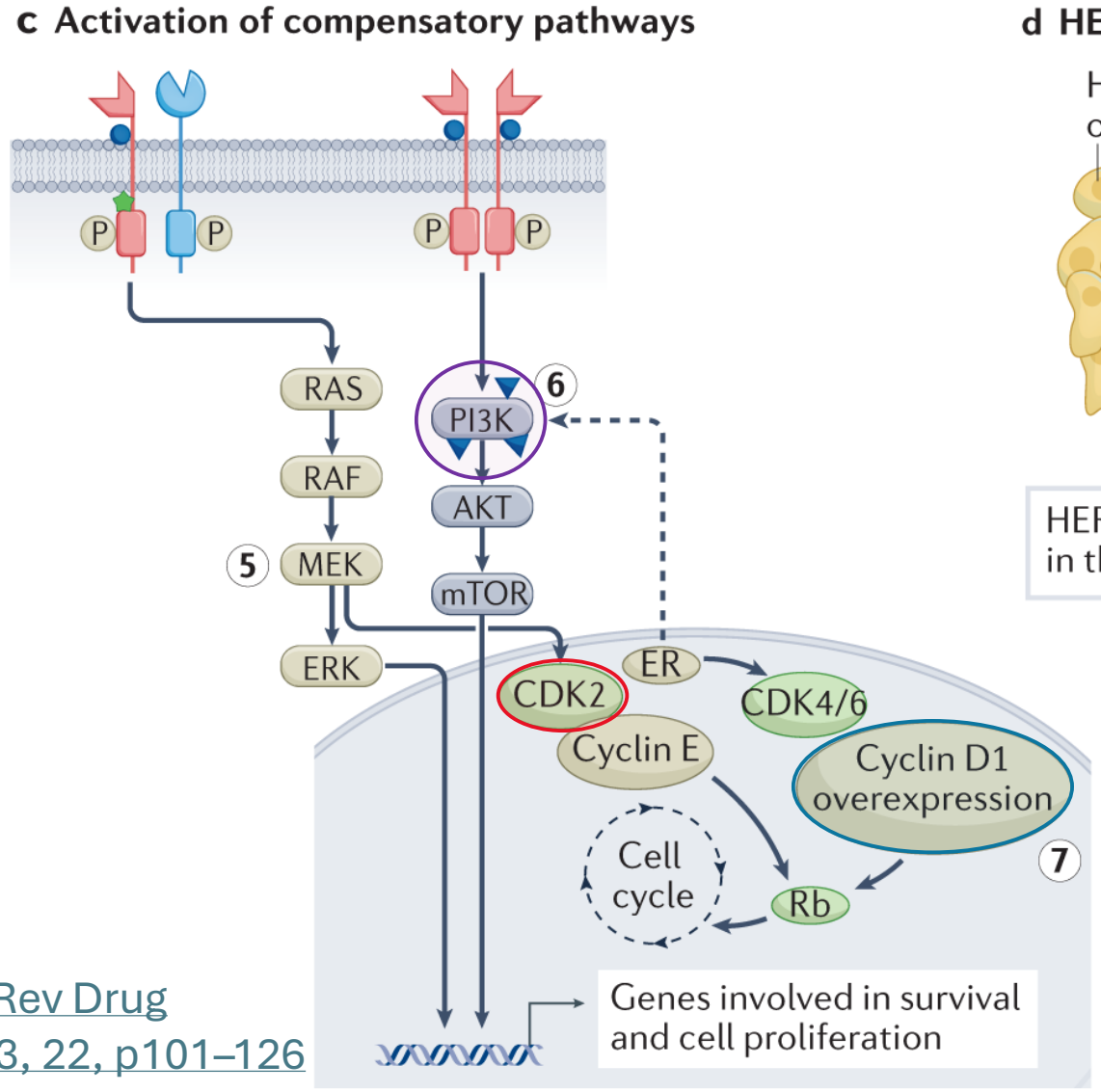


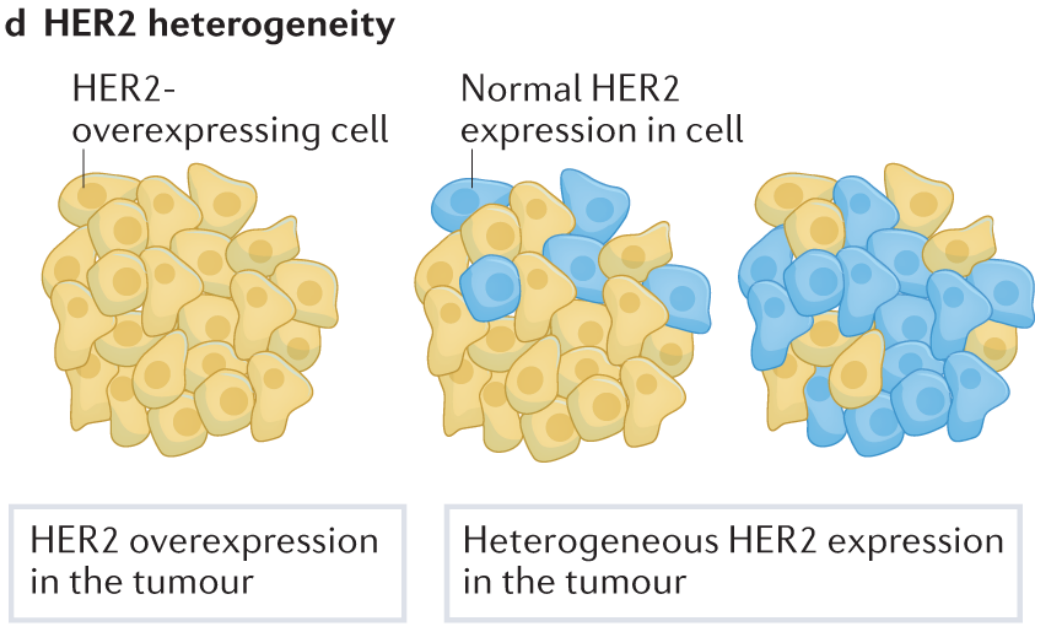


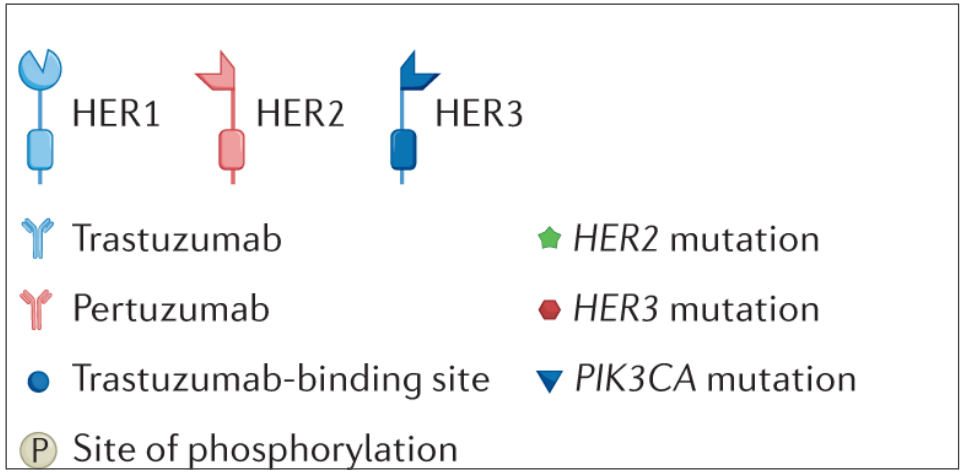


Swain, Nat Rev Drug DIscov, 2023, 22, p101–126

Mechanisms of HER2-targeted resistance (c-d)

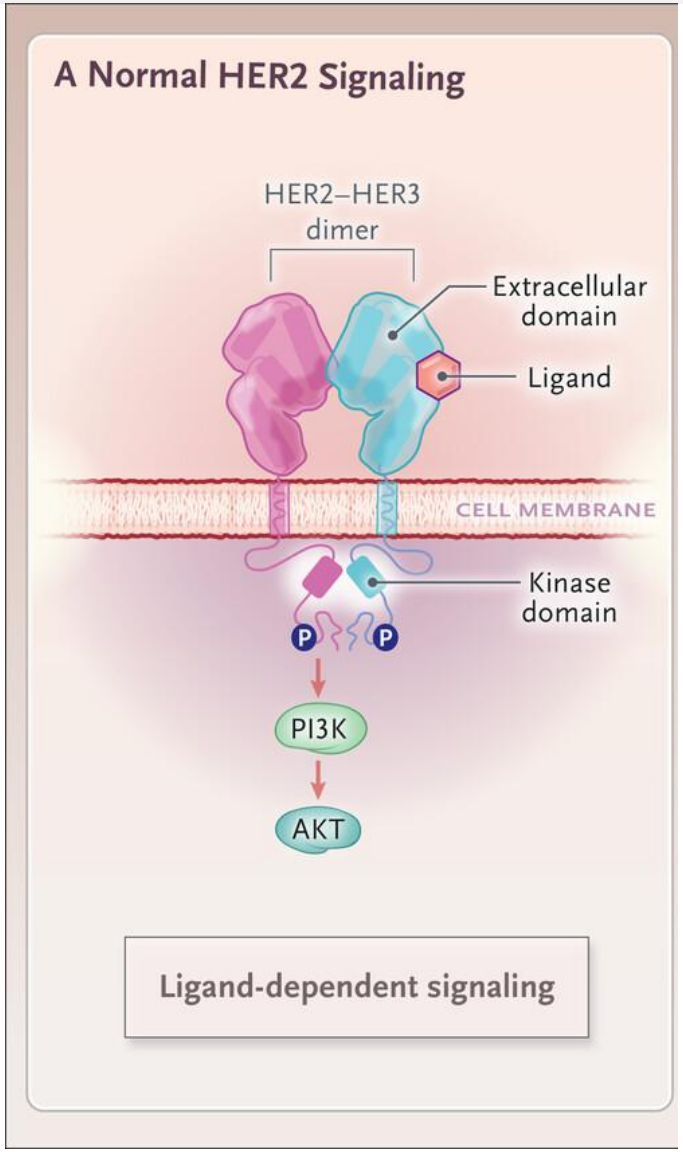




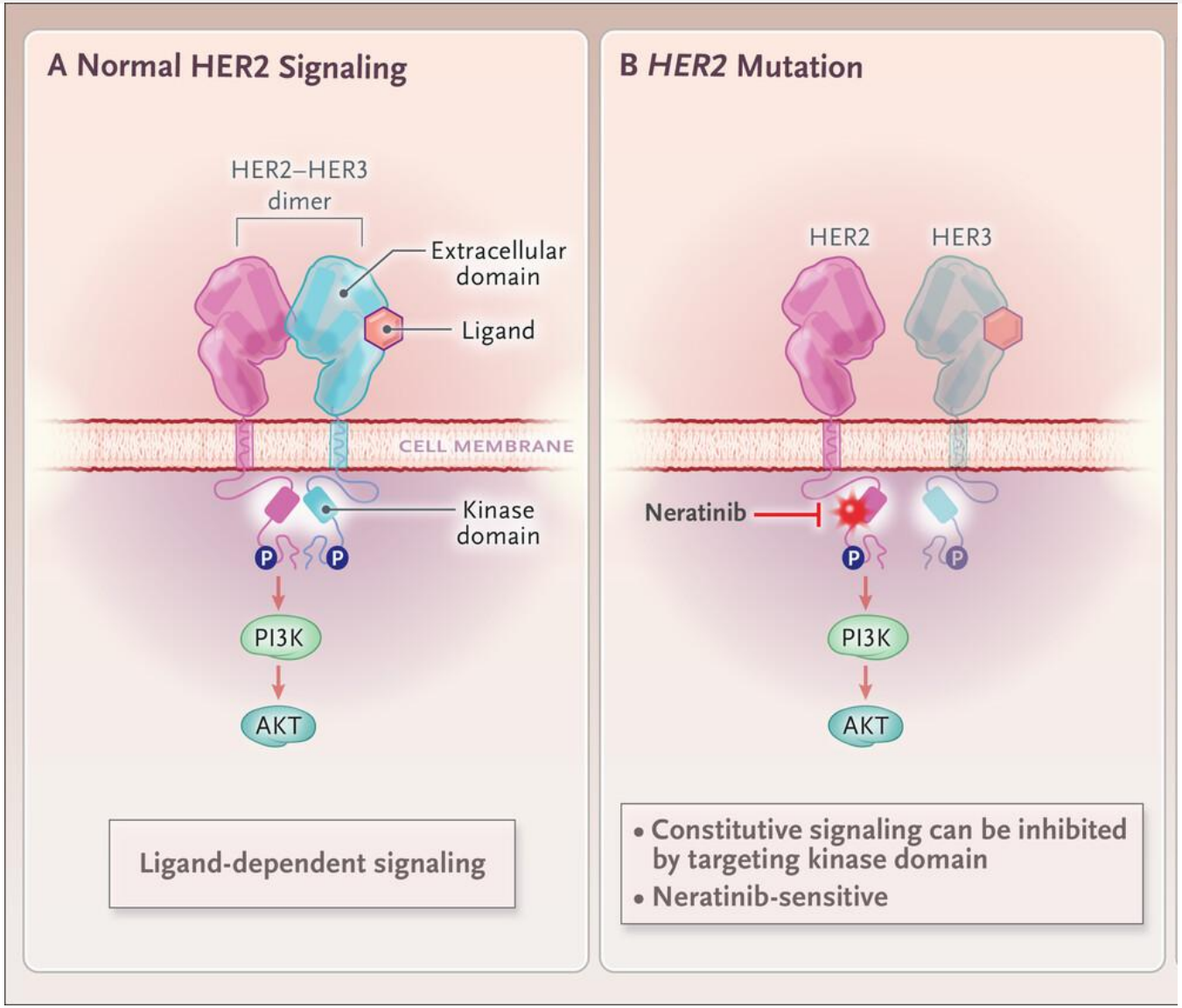


Swain, Nat Rev Drug DIscov, 2023, 22, p101–126

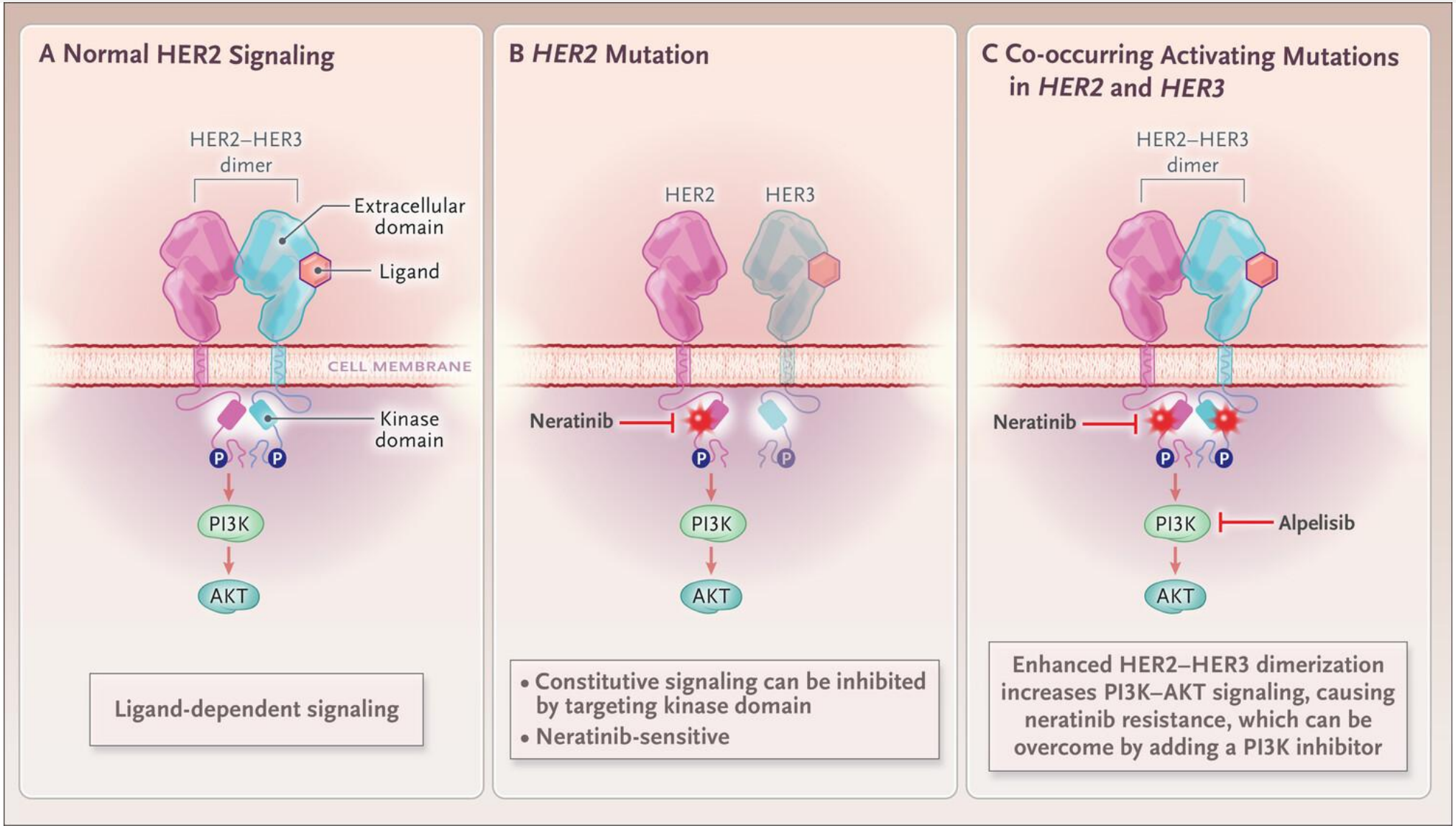
Resistance to HER2 Tyrosine Kinase Inhibition



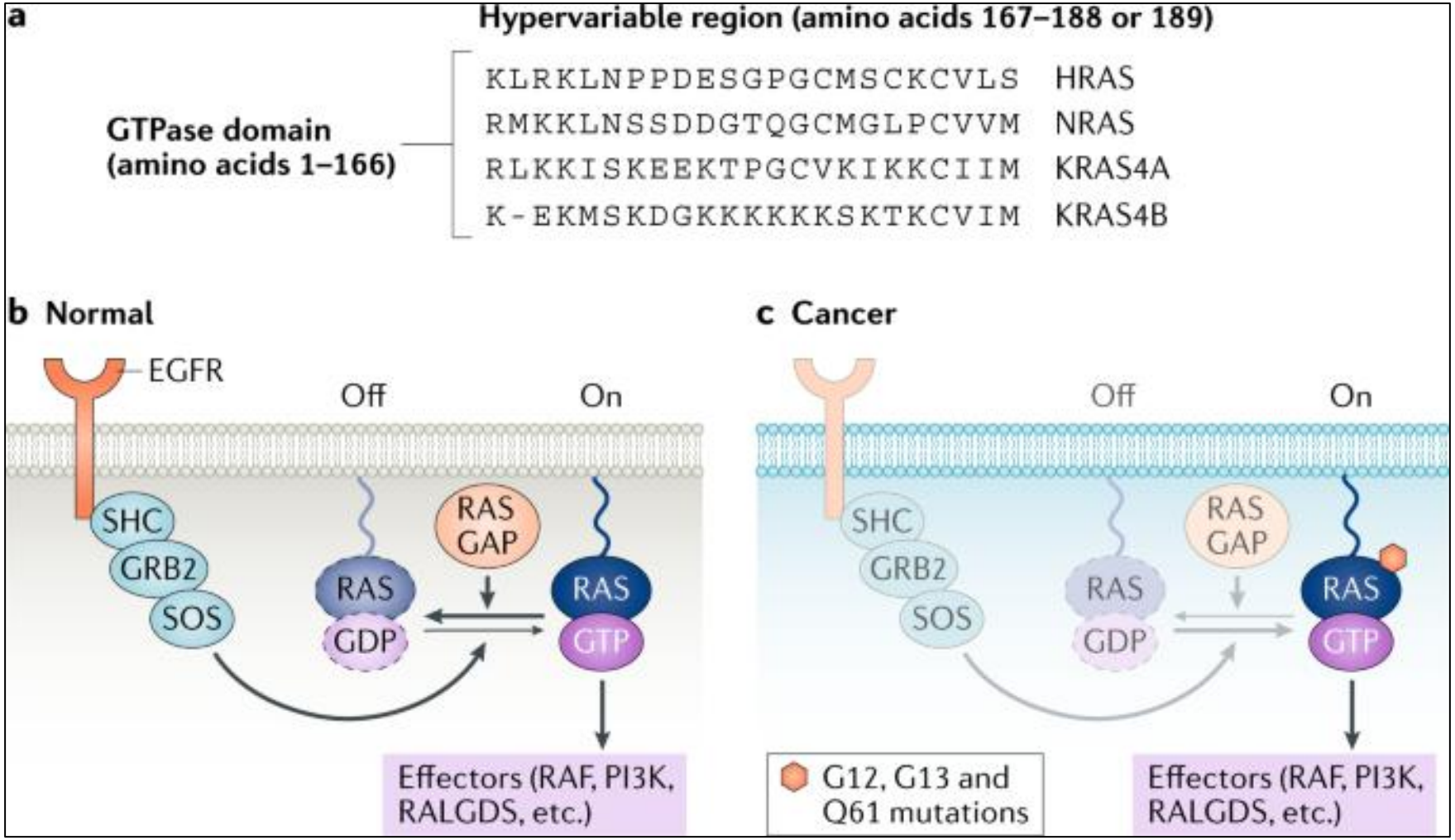
Resistance to HER2 Tyrosine Kinase Inhibition



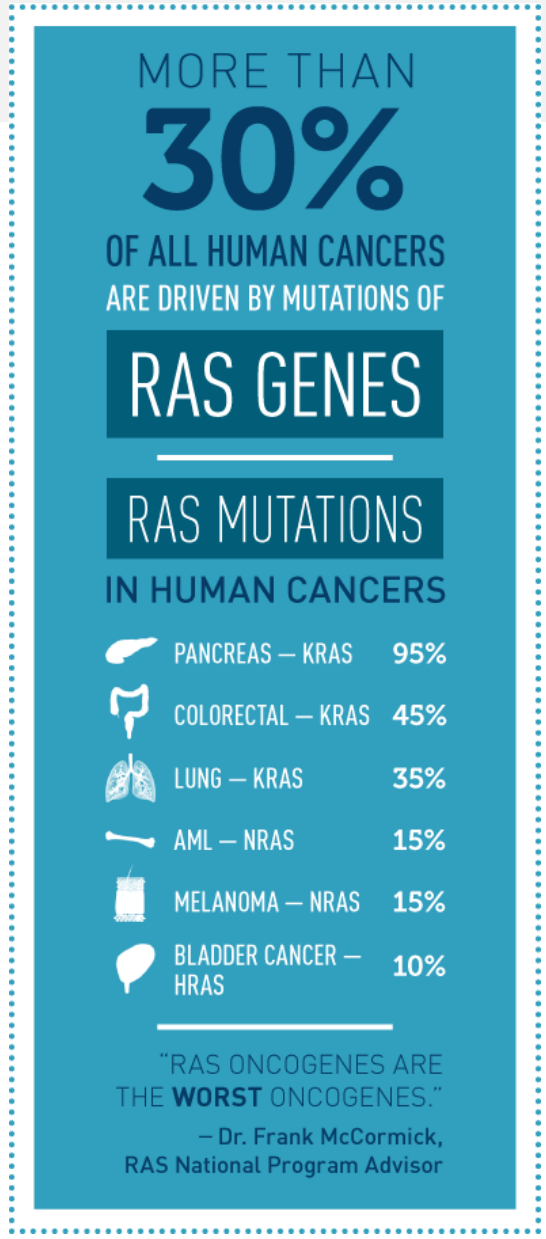
Resistance to HER2 Tyrosine Kinase Inhibition



RAS Mutations in Cancers

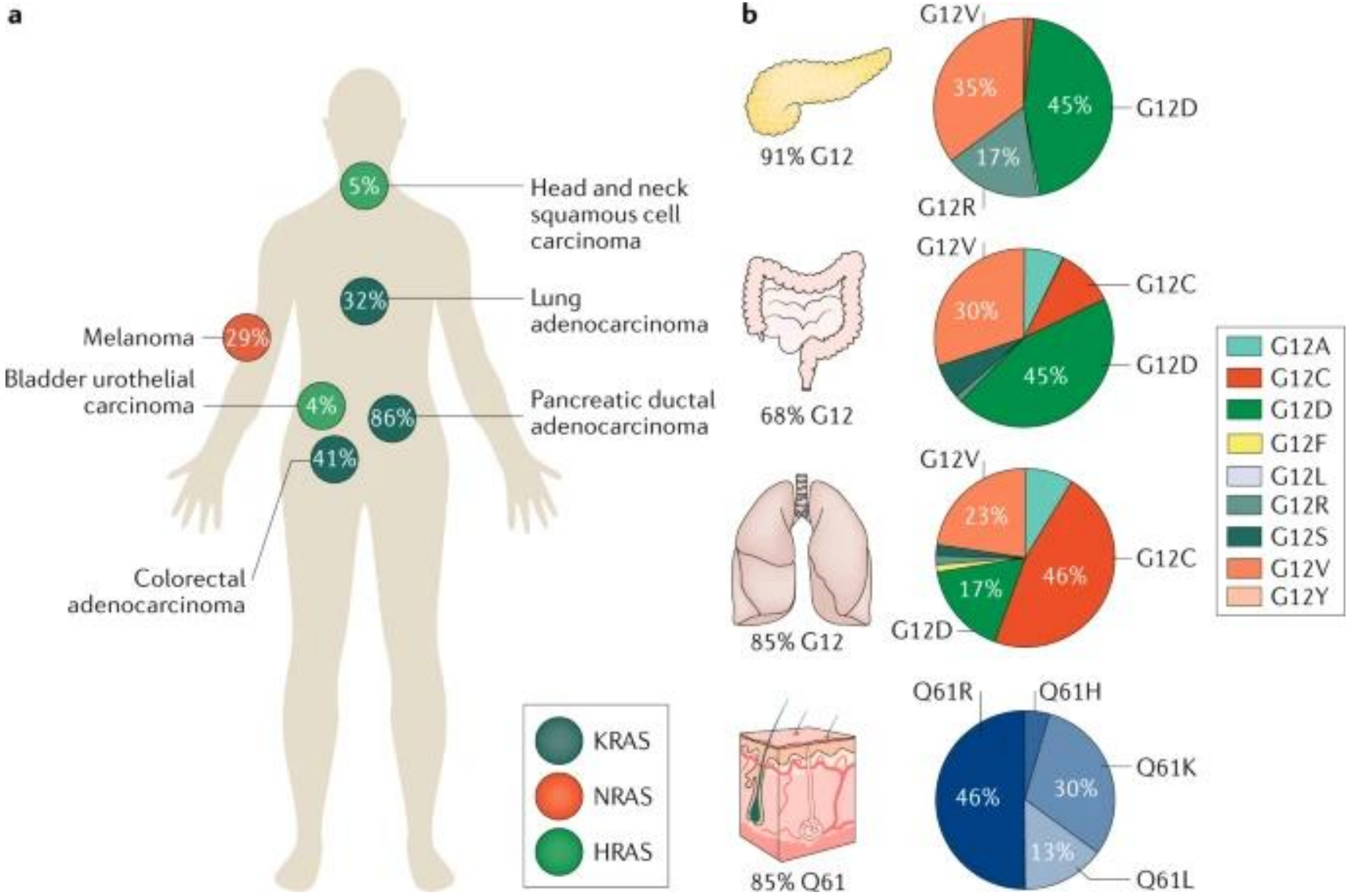


https://www.nature.com/articles/s41568-018-0076-6

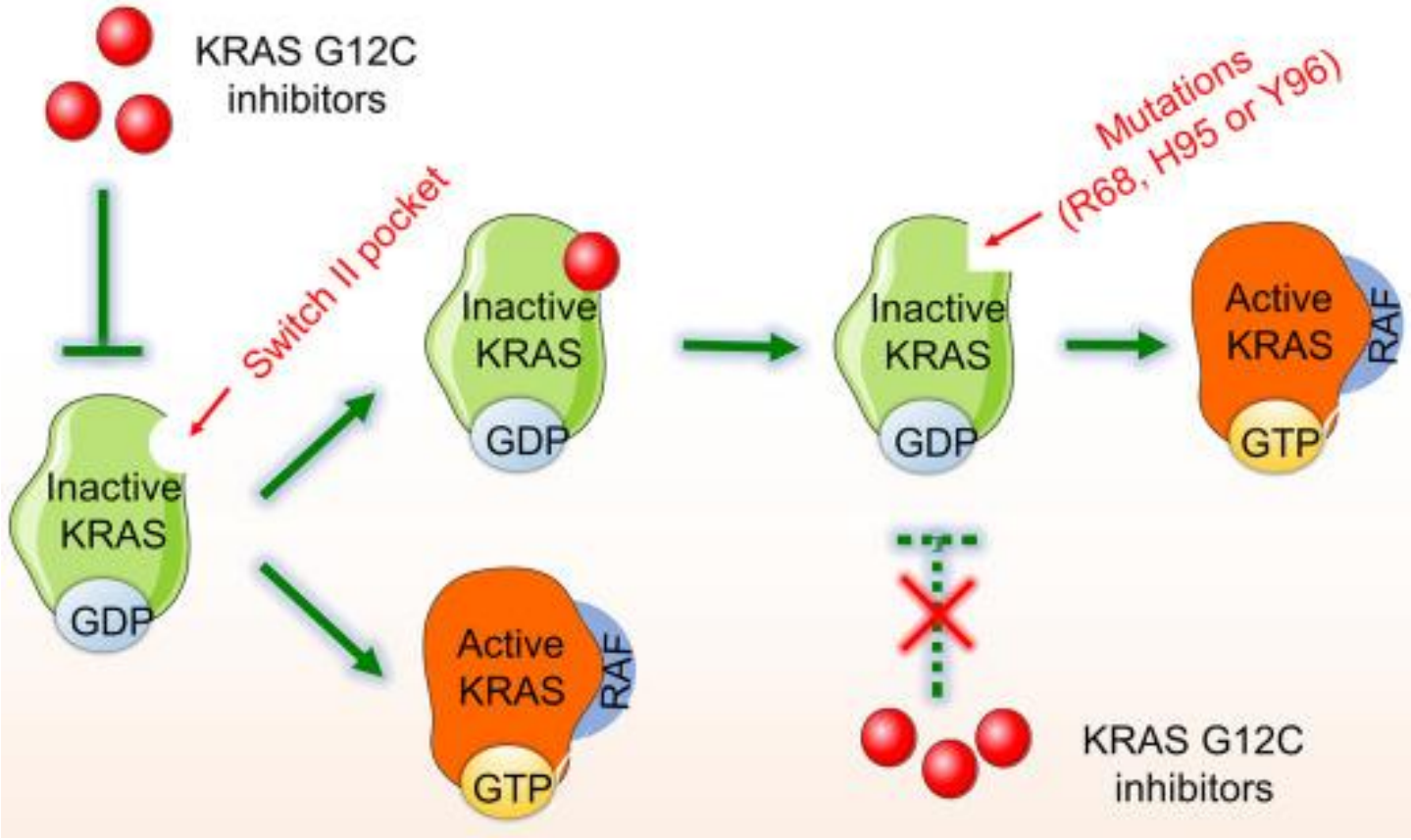


source: NCI-the ras initiatives

Frequency and distribution of RAS mutations in human cancers

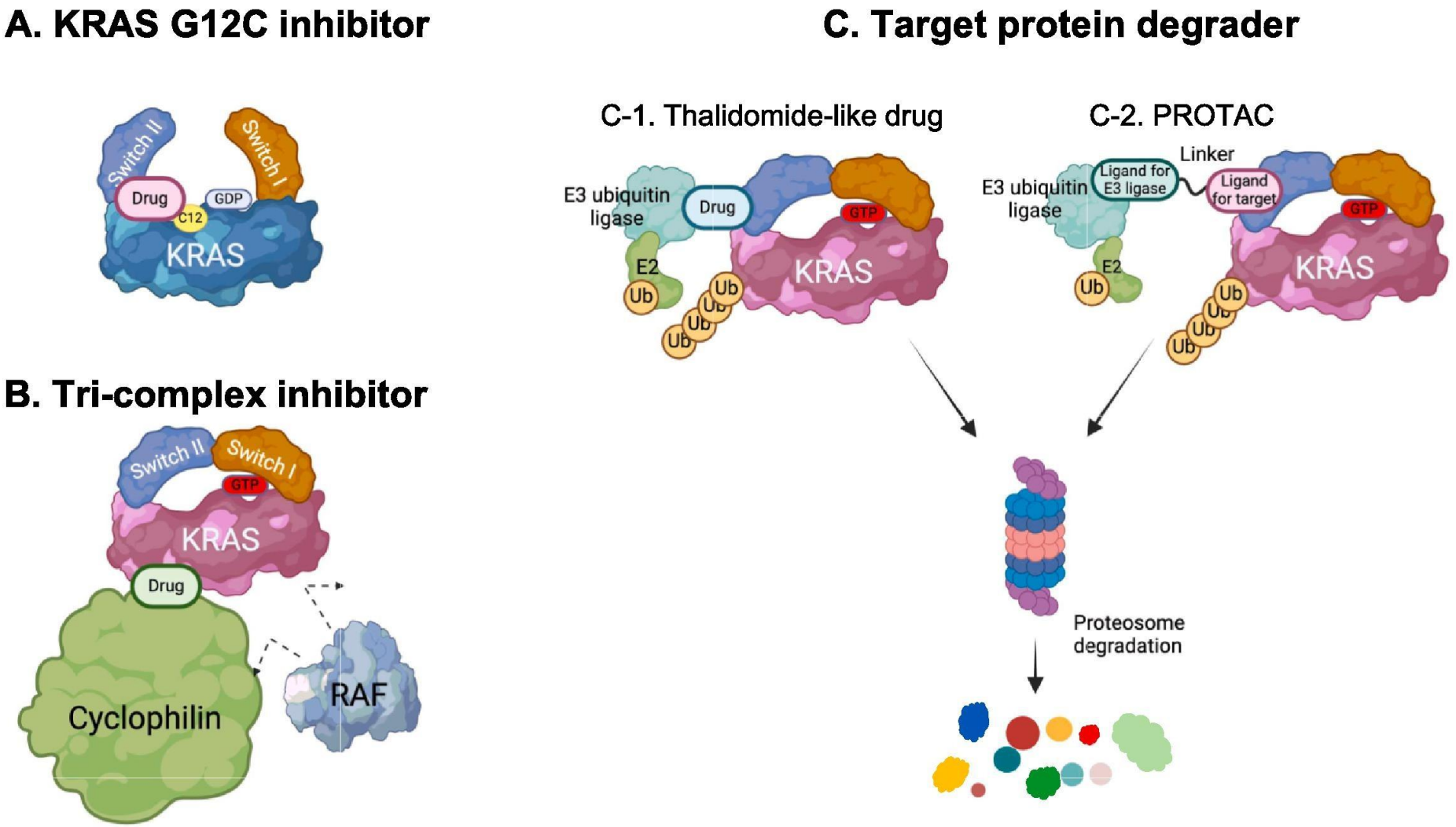


Resistance is all around again…



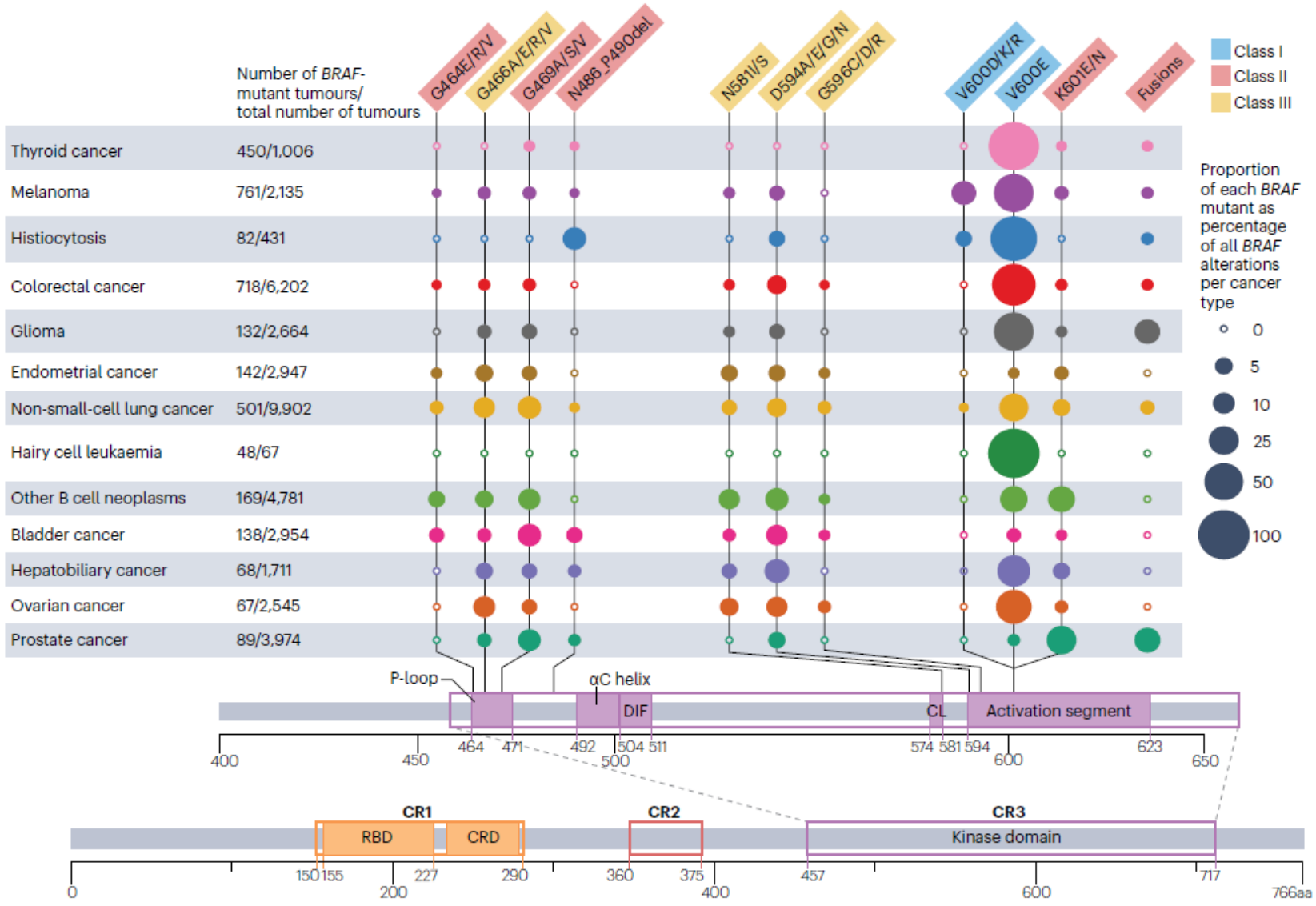
https://www.sciencedirect.com/science/article/pii/S0163725821002527

Drug mechanisms underlying KRAS inhibition



https://www.lungcancerjournal.info/article/S0169-5002%2824%2900420-3/fulltext

Frequency of BRAF mutations in human cancers

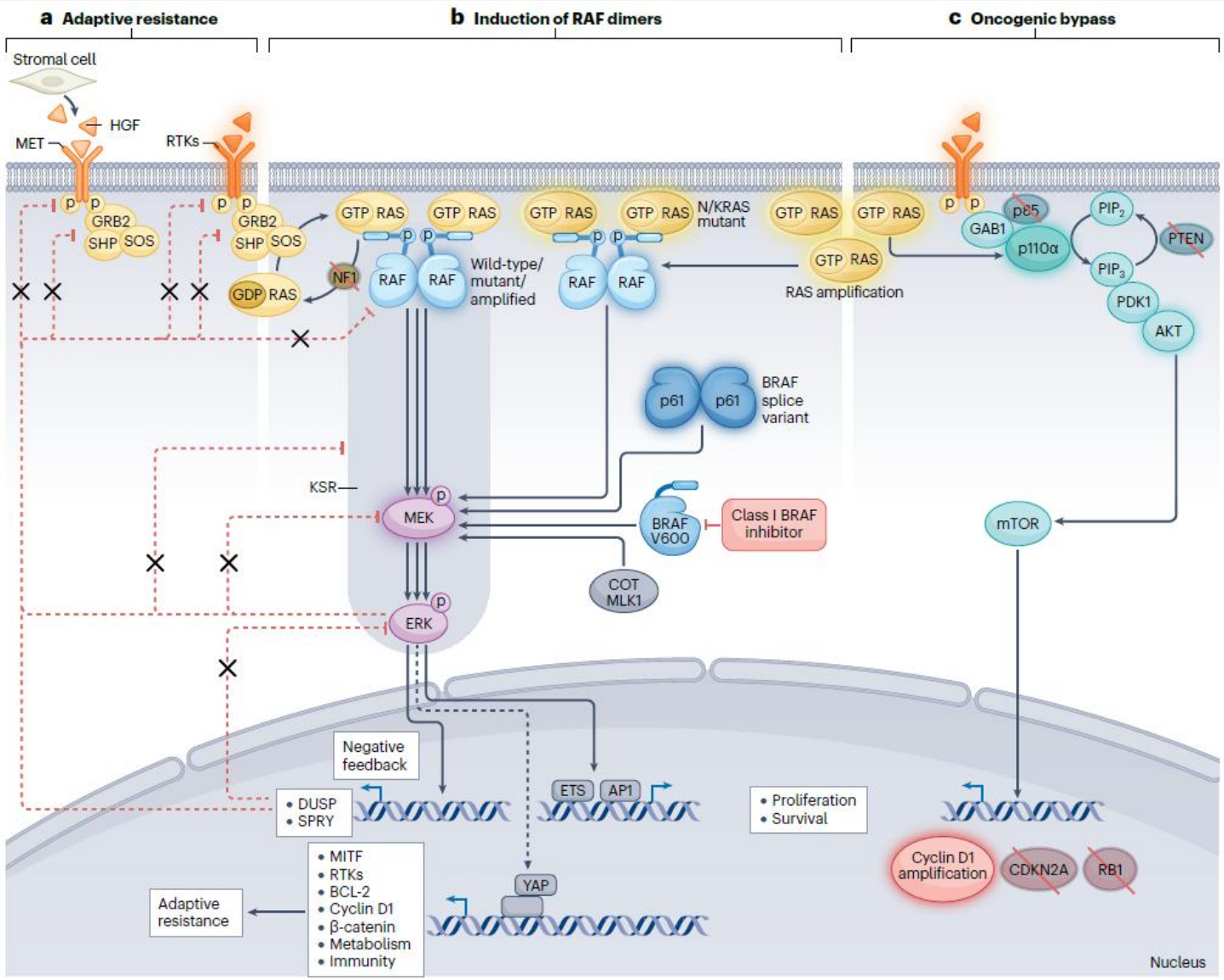


***BRAFV600E* among all alterations:**
melanoma (50%)
thyroid cancer (45%)
colon cancer (10%)
NSCLC (3%)

***BRAFV600E* among BRAF alterations:**
melanoma (90%)
thyroid cancer (95%)
colon cancer (90%)
NSCLC (60%)

https://www.nature.com/articles/s41571-023-00852-0

Mechanisms of BRAF inhibitor resistance



Melanoma patient with BRAFV600E mutation



Before treatment | 15 weeks post treatment | 22 weeks post treatment

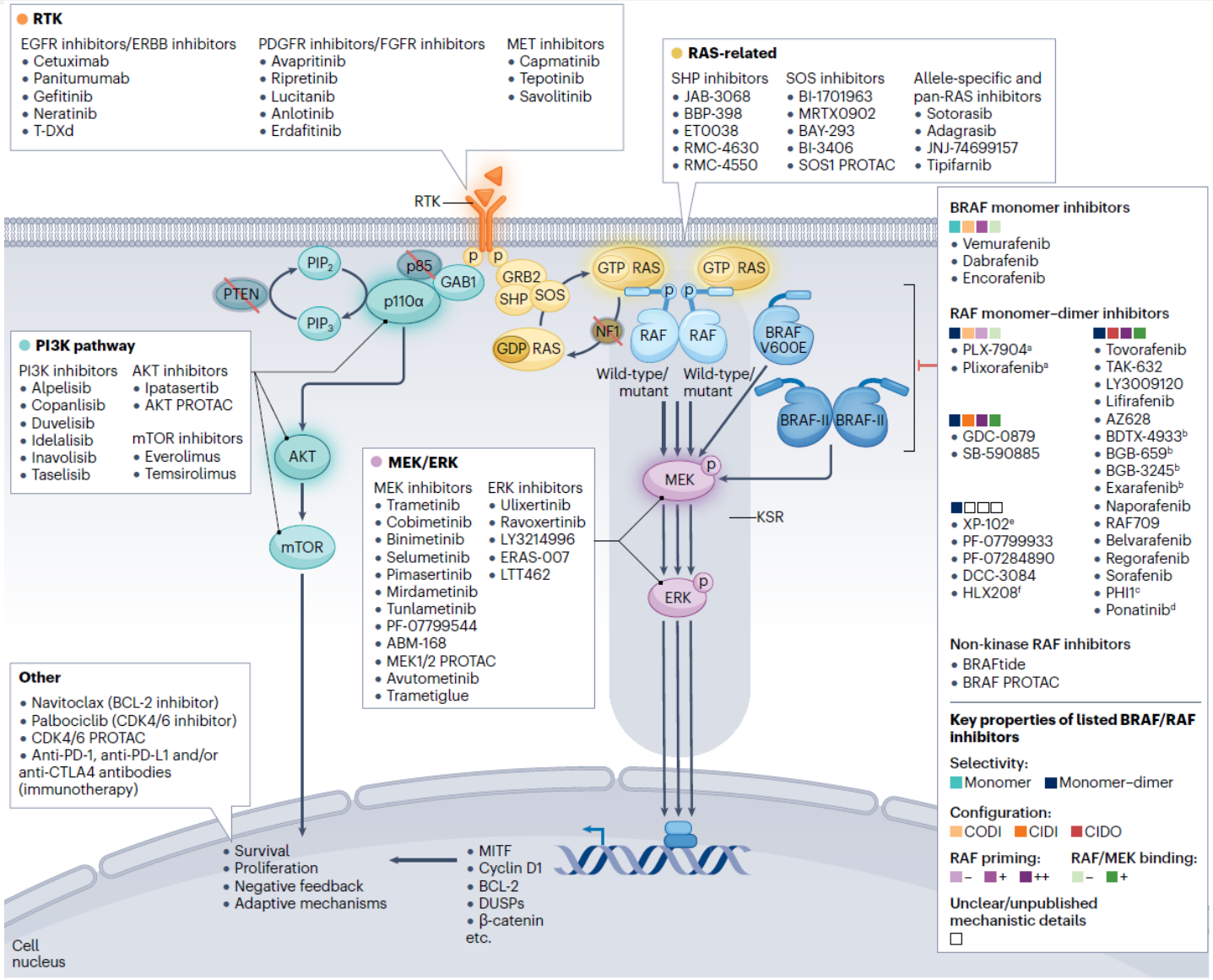
BRAF inhibitor resistance

I. rapid reactivation of ERK signalling, due to **relief of negative feedback mechanisms**, that results in adaptive (re)activation of RTK signalling, RAS activation and RAF dimerization, or

II. through genetic alterations such as **NRAS mutations**, **BRAF amplification** and **expression of BRAF splice variants** that promote RAF dimer formation

https://www.nature.com/articles/s41571-023-00852-0

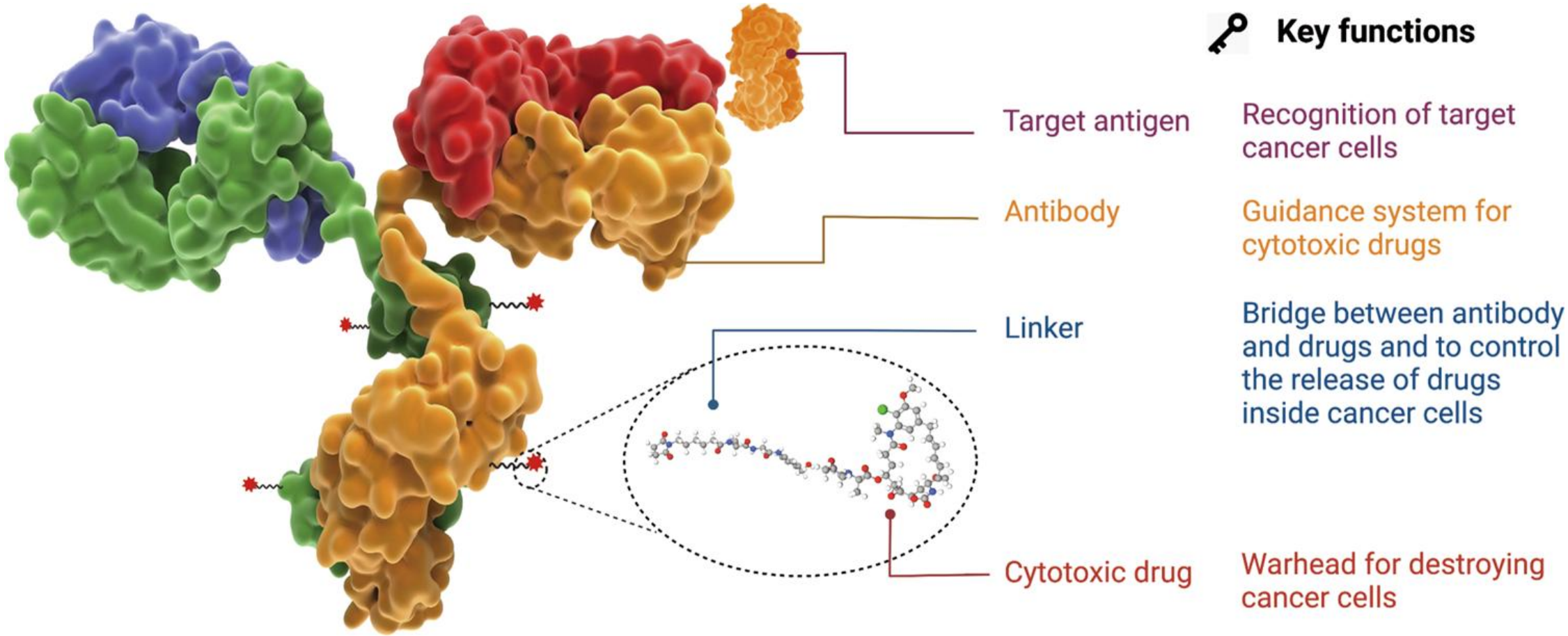
Therapeutic strategies to overcome resistance to RAF inhibitors



https://www.nature.com/articles/s41571-023-00852-0

Types of Targeted Therapies: ADC

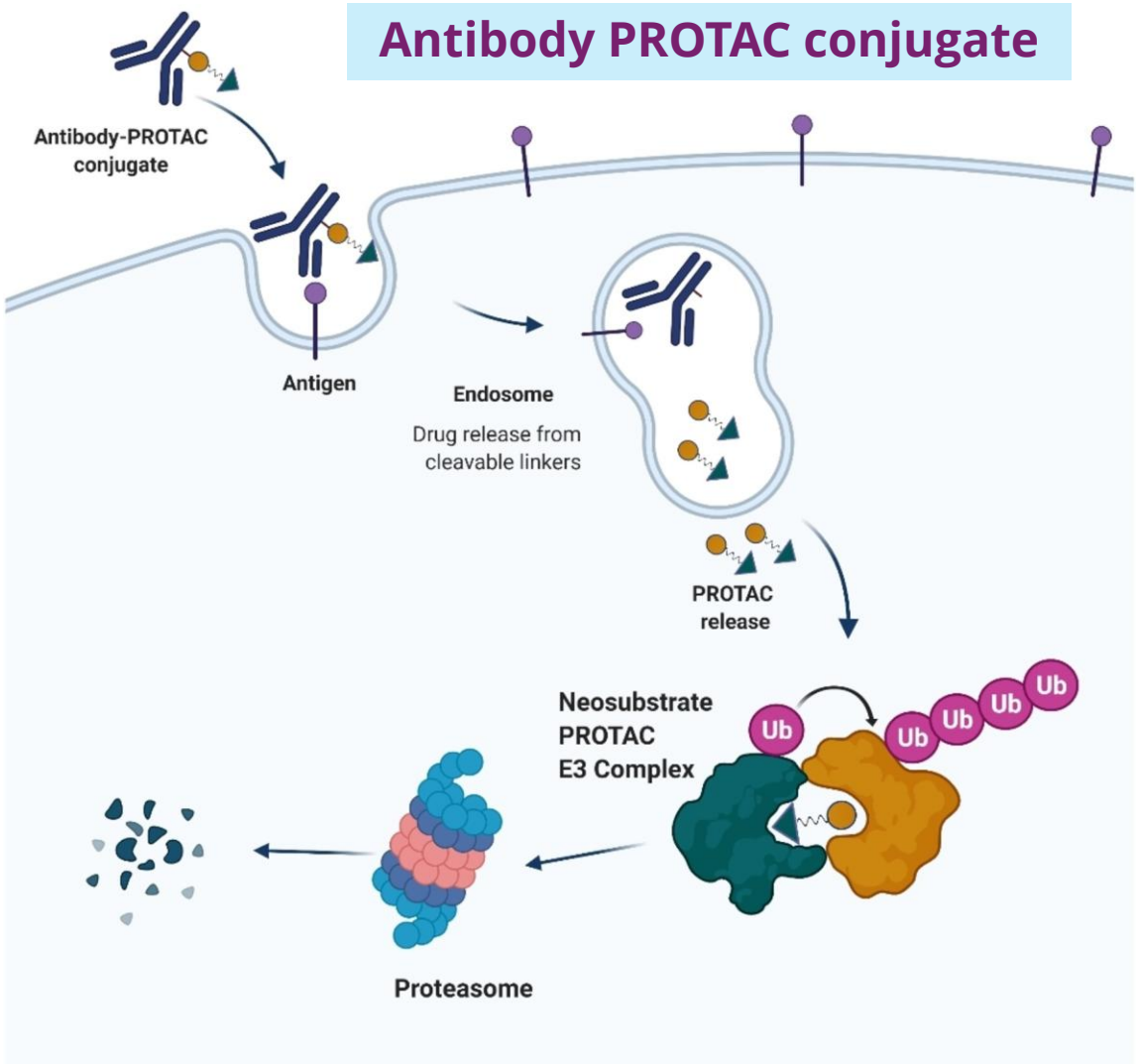
Antibody–drug conjugate (ADC) is typically composed of a monoclonal antibody (mAb) covalently attached to a cytotoxic drug via a chemical linker



https://www.nature.com/articles/s41392-022-00947-7

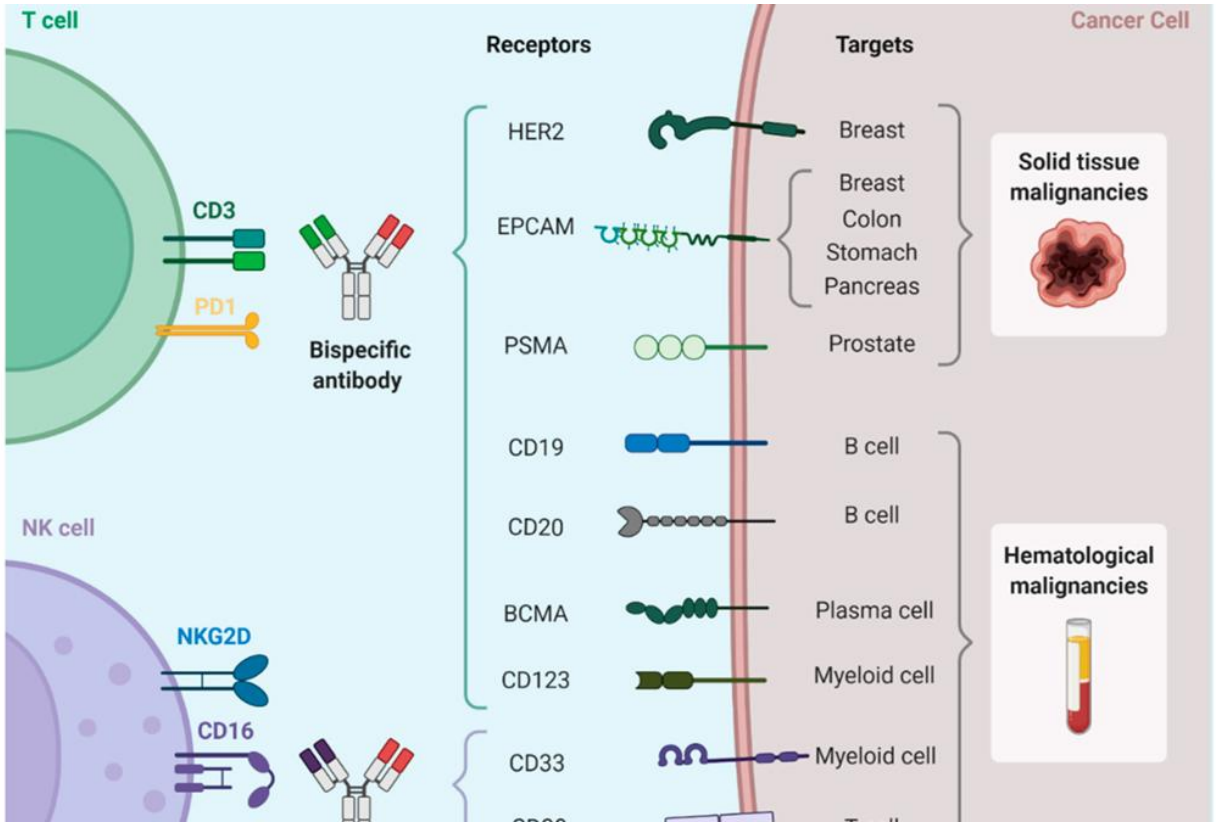
Types of Targeted Therapies: PROTACs

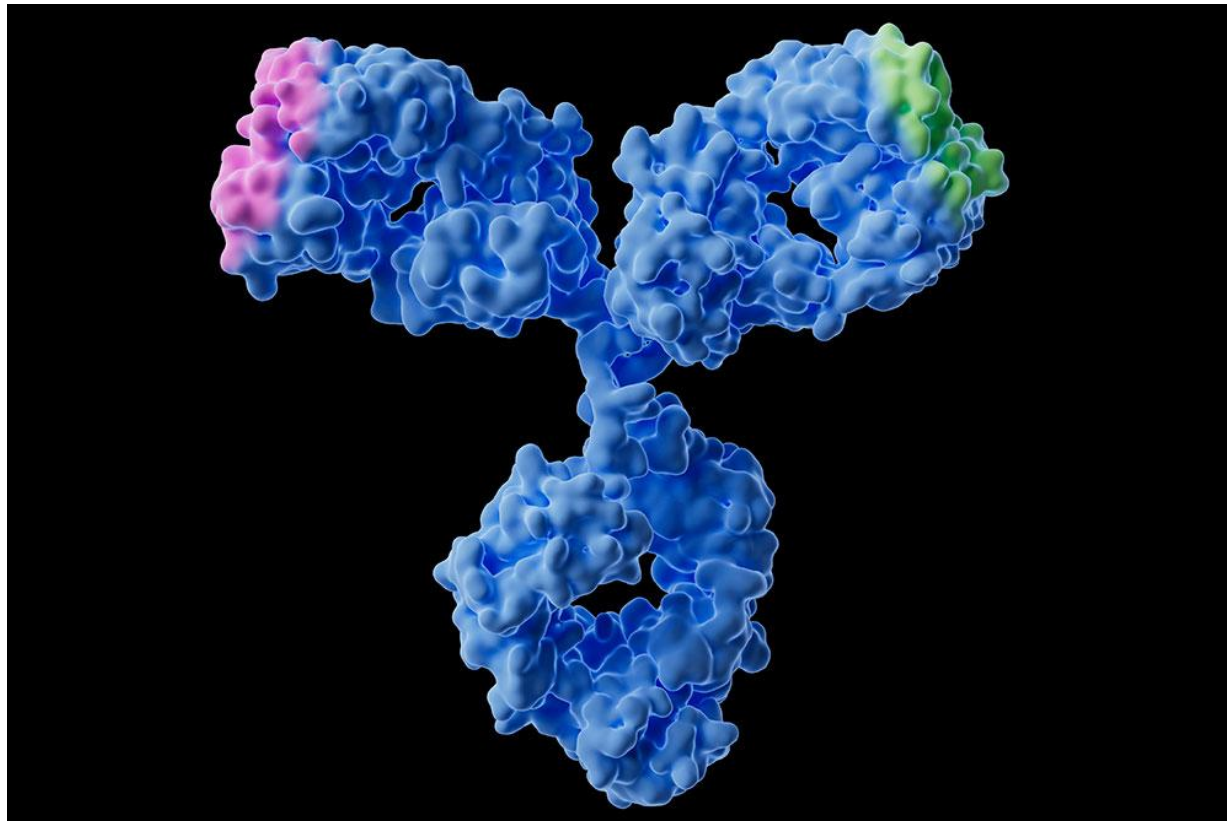
- ✓ **Καταστρέφει την πρωτεΐνη αντί απλώς να εμποδίζει τη δραστηριότητά της.**
- ✓ **Λειτουργεί σε «μη φαρμακευτικούς» στόχους, συμπεριλαμβανομένων των μεταγραφικών παραγόντων και των πρωτεϊνών του ικριώματος.**
- ✓ **Μπορεί να ξεπεράσει την αντοχή στα φάρμακα, ειδικά σε καρκίνους όπου οι μεταλλάξεις καθιστούν τους παραδοσιακούς αναστολείς αναποτελεσματικούς.**
- ✓ **Δρα καταλυτικά - ένα μόριο PROTAC μπορεί να αποικοδομήσει πολλαπλά αντίγραφα του στόχου.**

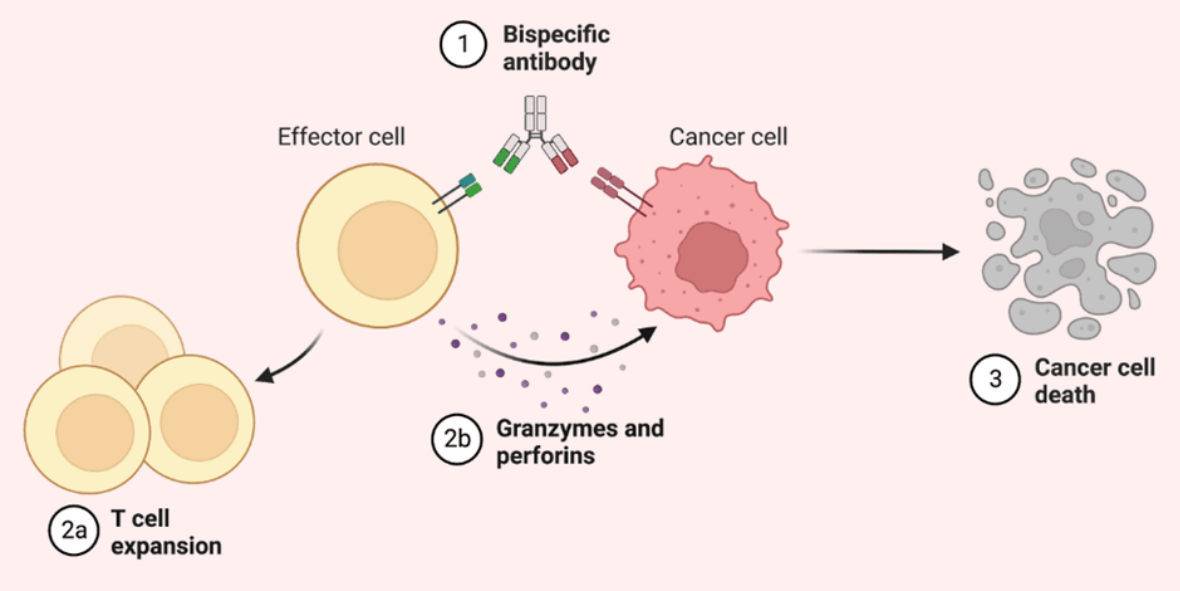


https://chemistry-europe.onlinelibrary.wiley.com/doi/10.1002/cbic.202100270

Types of Targeted Therapies: Bispecific Abs







- Τα BsAbs συνήθως λειτουργούν με:
- Γεφύρωση των κυττάρων του ανοσοποιητικού με τα καρκινικά κύτταρα:
- Ο ένας βραχίονας συνδέεται με ένα αντιγόνο που σχετίζεται με τον όγκο (π.χ. CD19, BCMA).
- Το άλλο συνδέεται με το CD3 στα Τ κύτταρα, ενεργοποιώντας τα για να σκοτώσουν το καρκινικό κύτταρο.
- Διπλός αποκλεισμός:
- Ορισμένα BsAbs στοχεύουν δύο υποδοχείς σηματοδότησης (π.χ. EGFR + MET) για να κλείσουν τις περιττές οδούς ανάπτυξης.
- Ενισχυμένη ειδικότητα:
- Απαιτώντας δύο αντιγόνα για δέσμευση, το BsAbs μπορεί να μειώσει τις επιδράσεις εκτός στόχου.