

Drilling Down on Molecular Targeted Approaches to Therapy

Professor Peter Schmid, MD PhD FRCP

Lead, Centre for Experimental Cancer Medicine
Barts Cancer Institute, St Bartholomew's Hospital
Queen Mary University of London

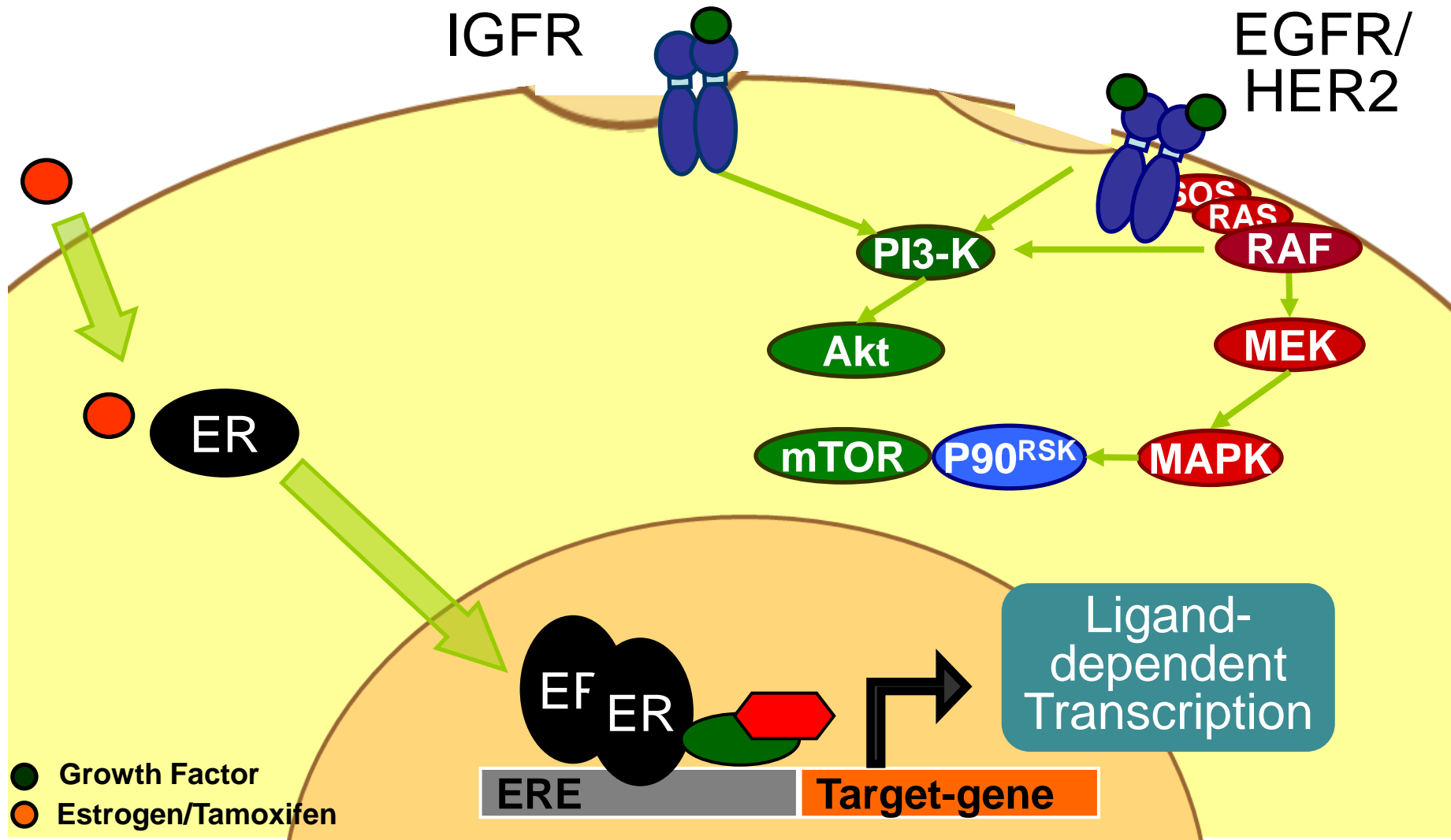


Molecular Targeted Approaches to Therapy in MBC

- Key molecular pathways in MBC
 - ER signaling, PI3K/mTOR, cyclin D/CDK4/6
 - HER2 and HER3
 - DNA damage repair
 - Immune checkpoints
- Pathway adaptation over time and therapeutic implications
- Mutation analysis and biomarkers to select targeted treatments

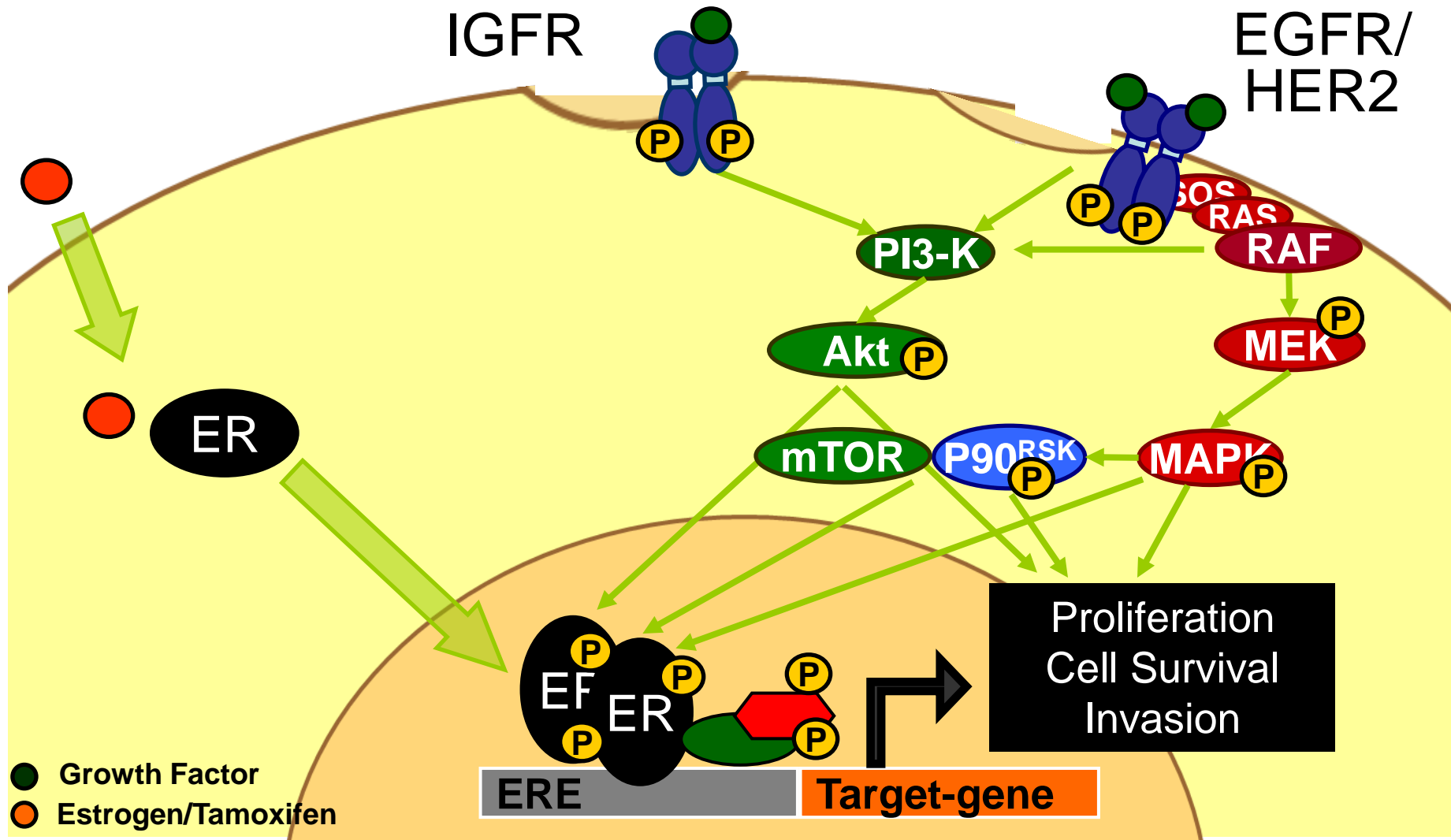
ER-Signaling and Anti-oestrogen Therapy

Understanding the Cellular Signaling Network



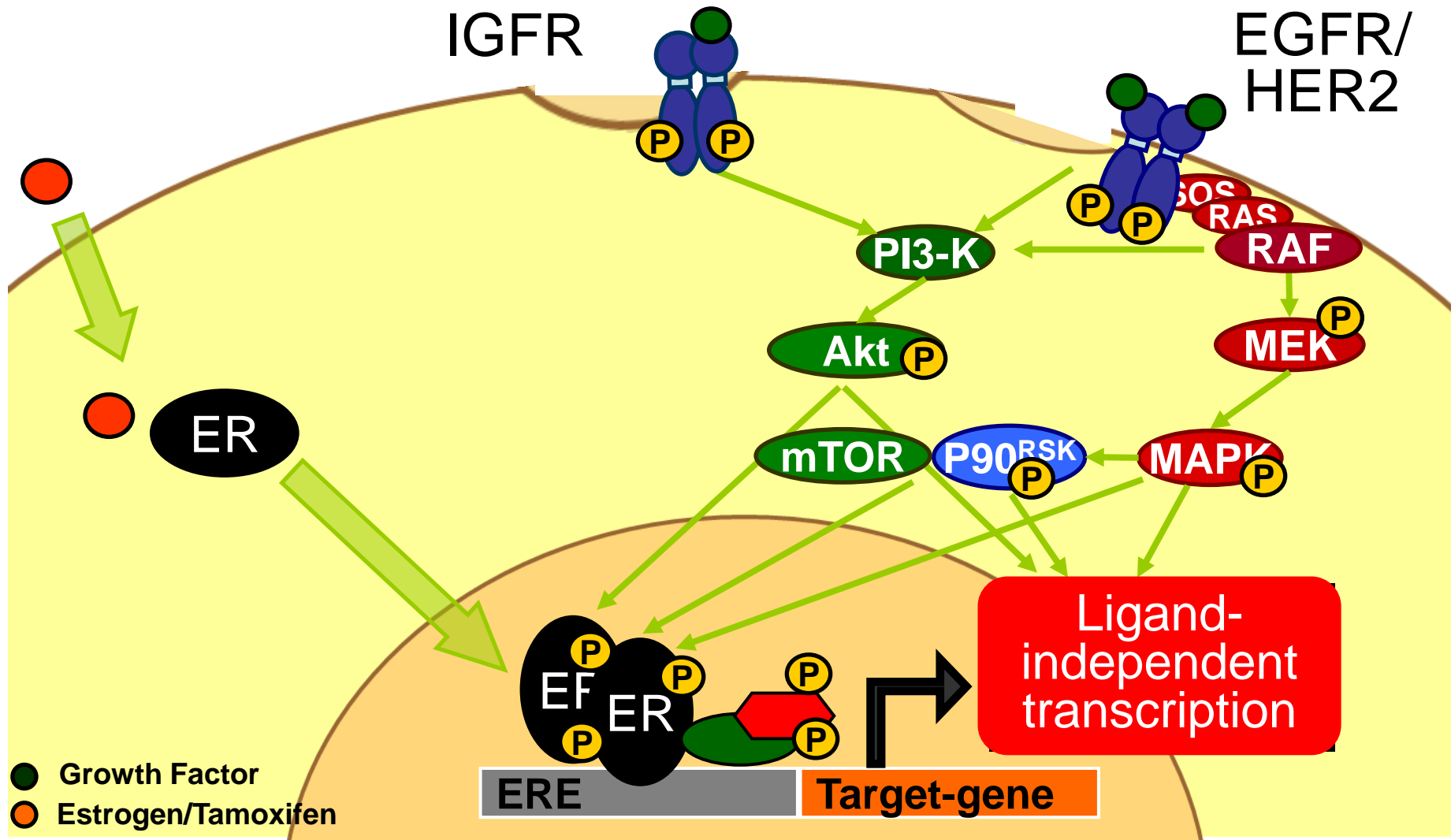
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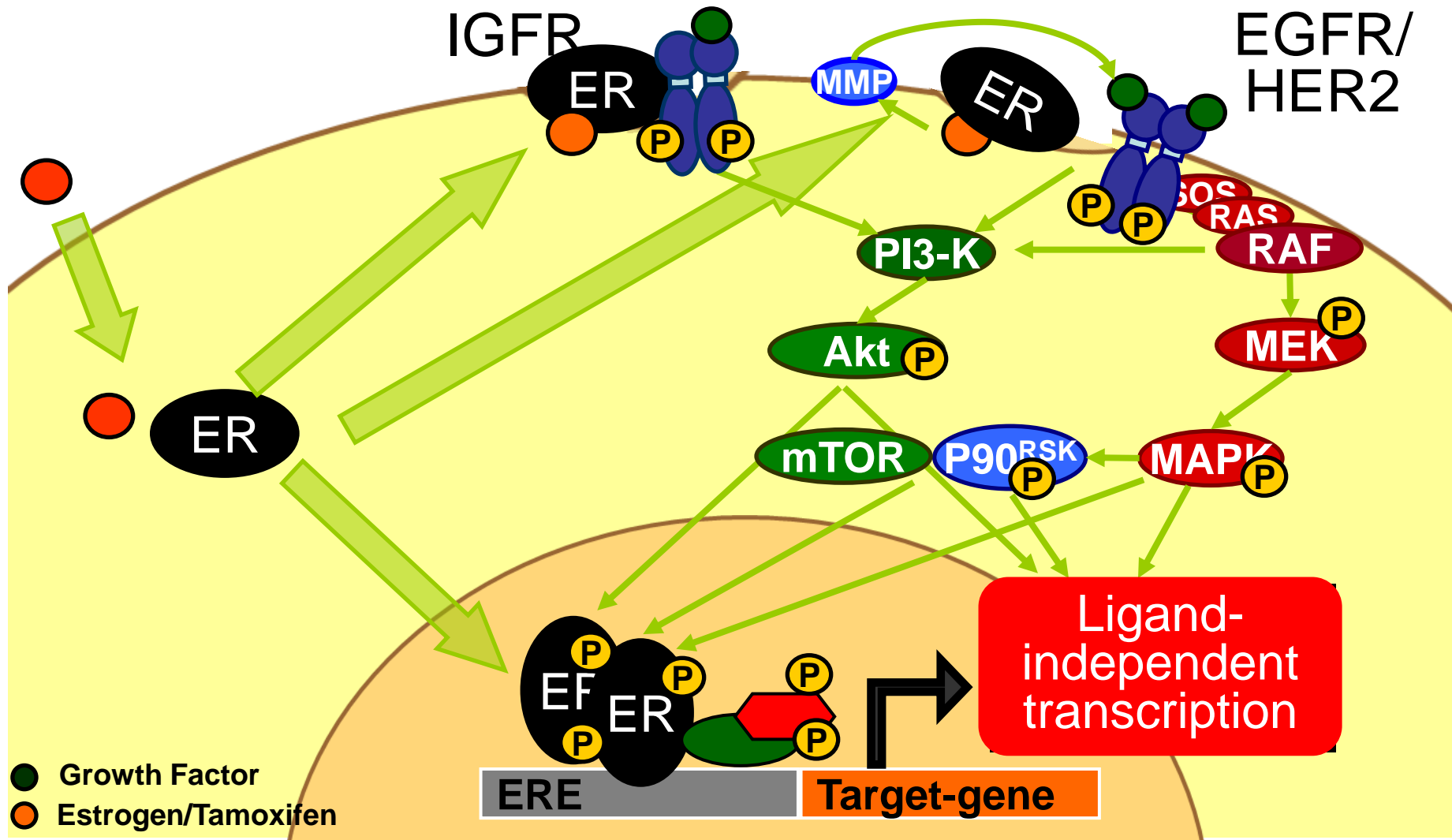
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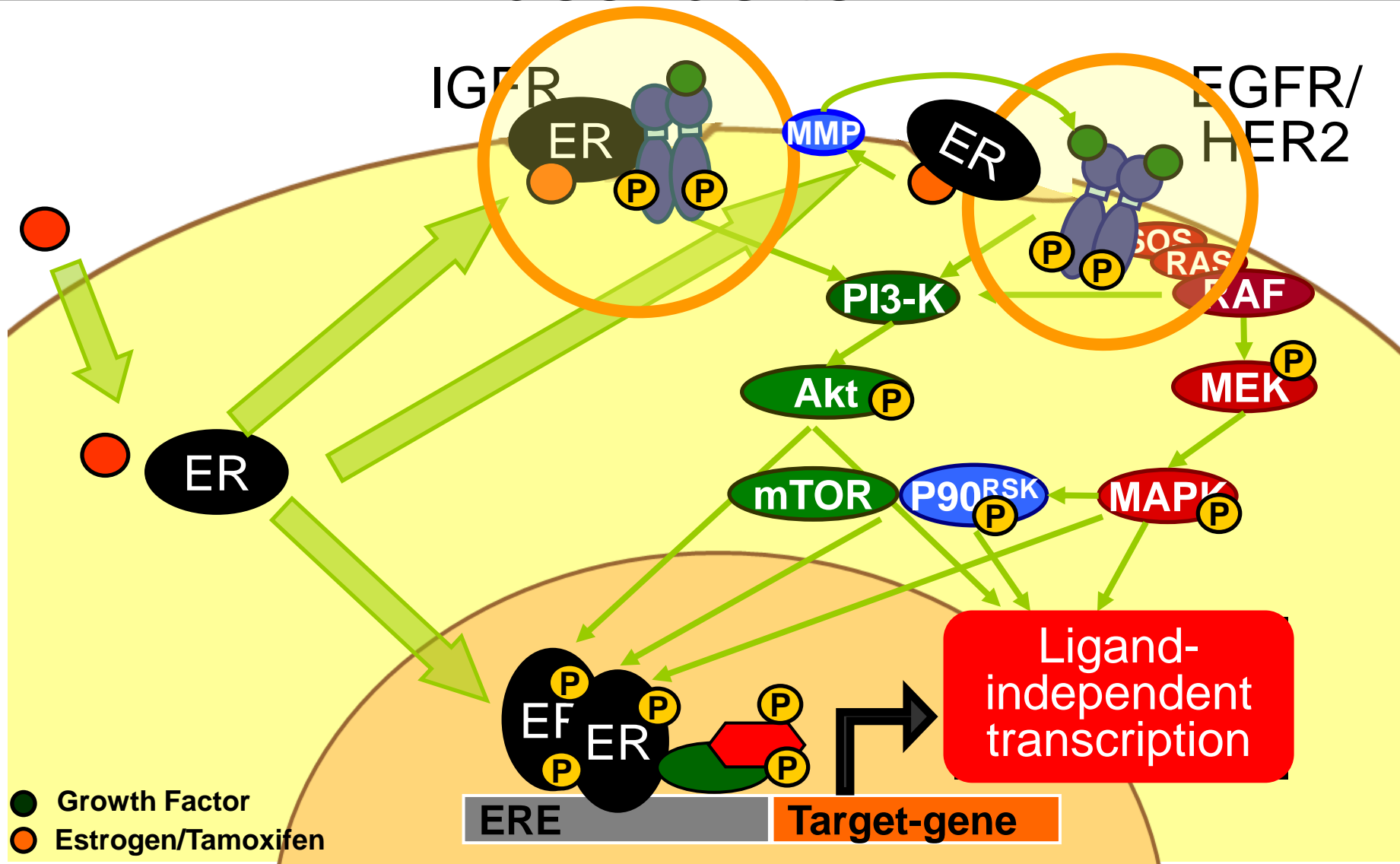
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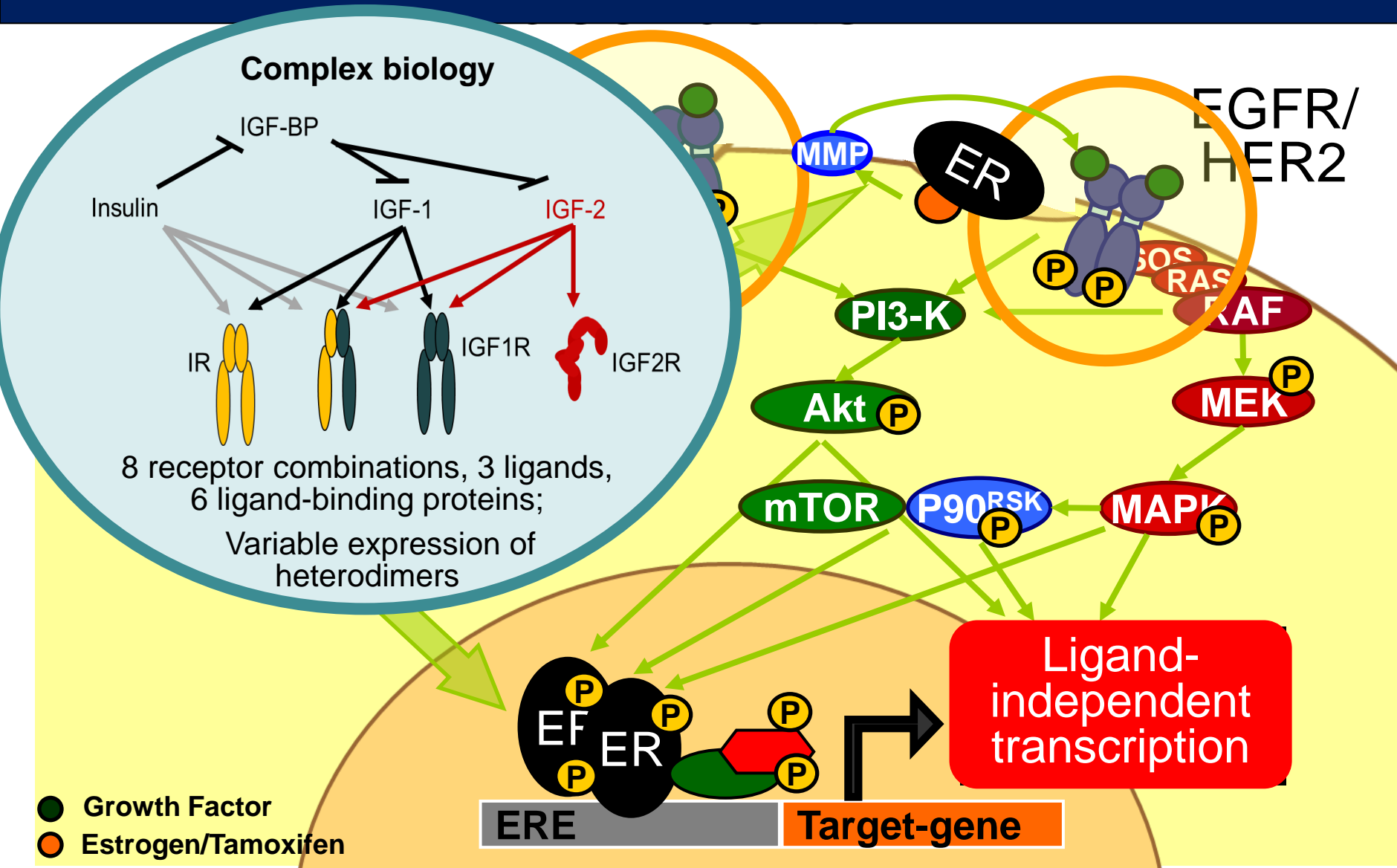
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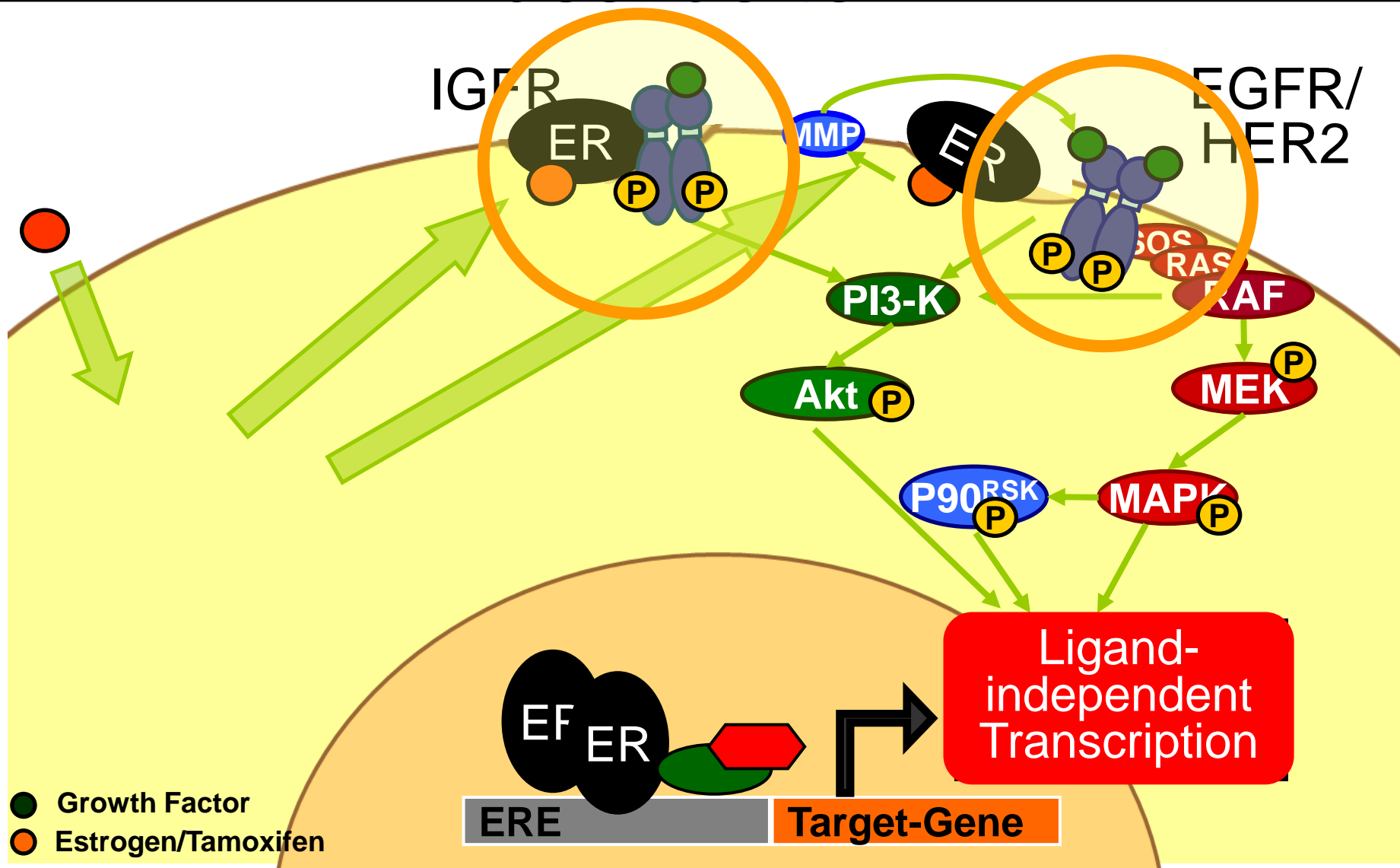
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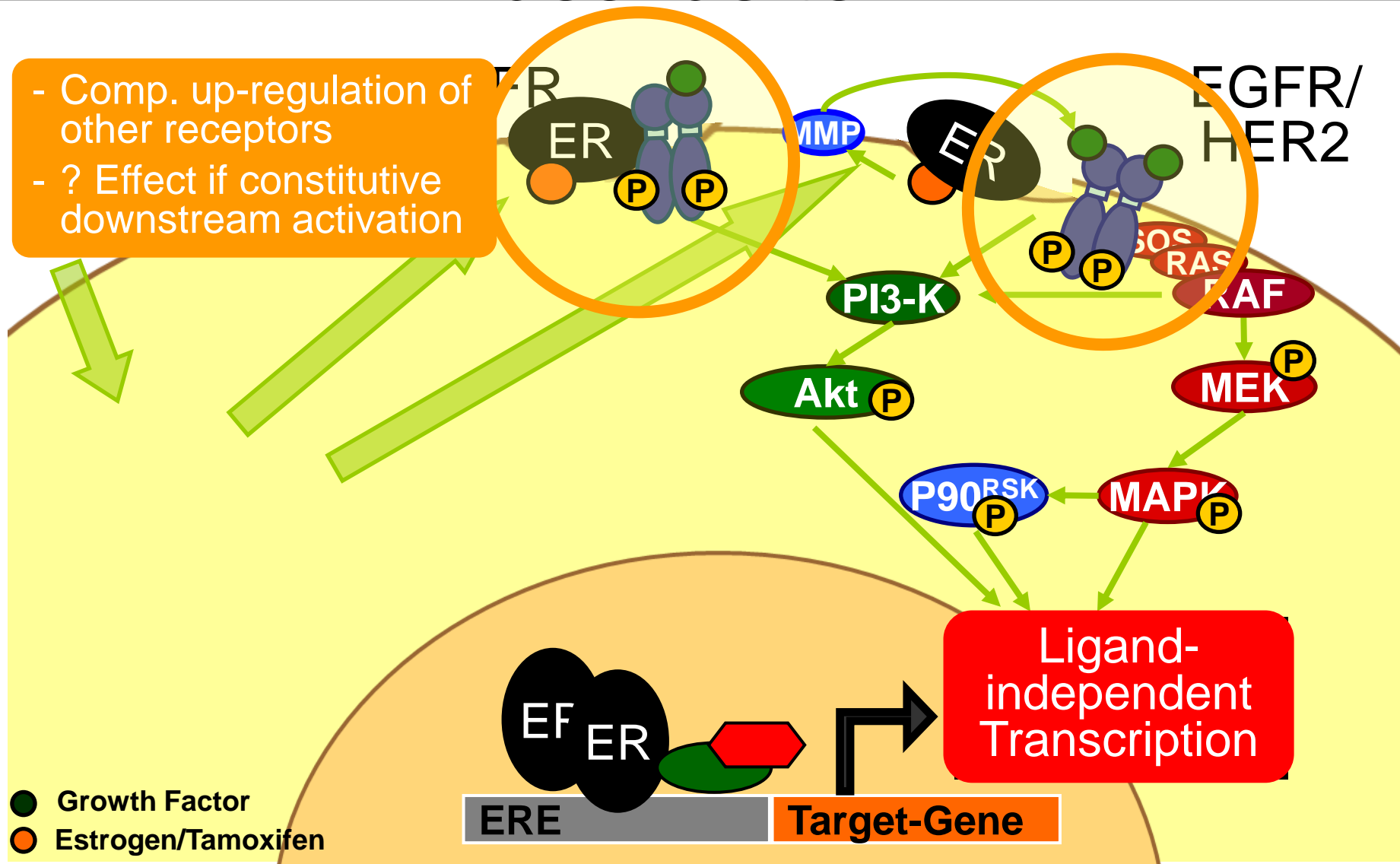
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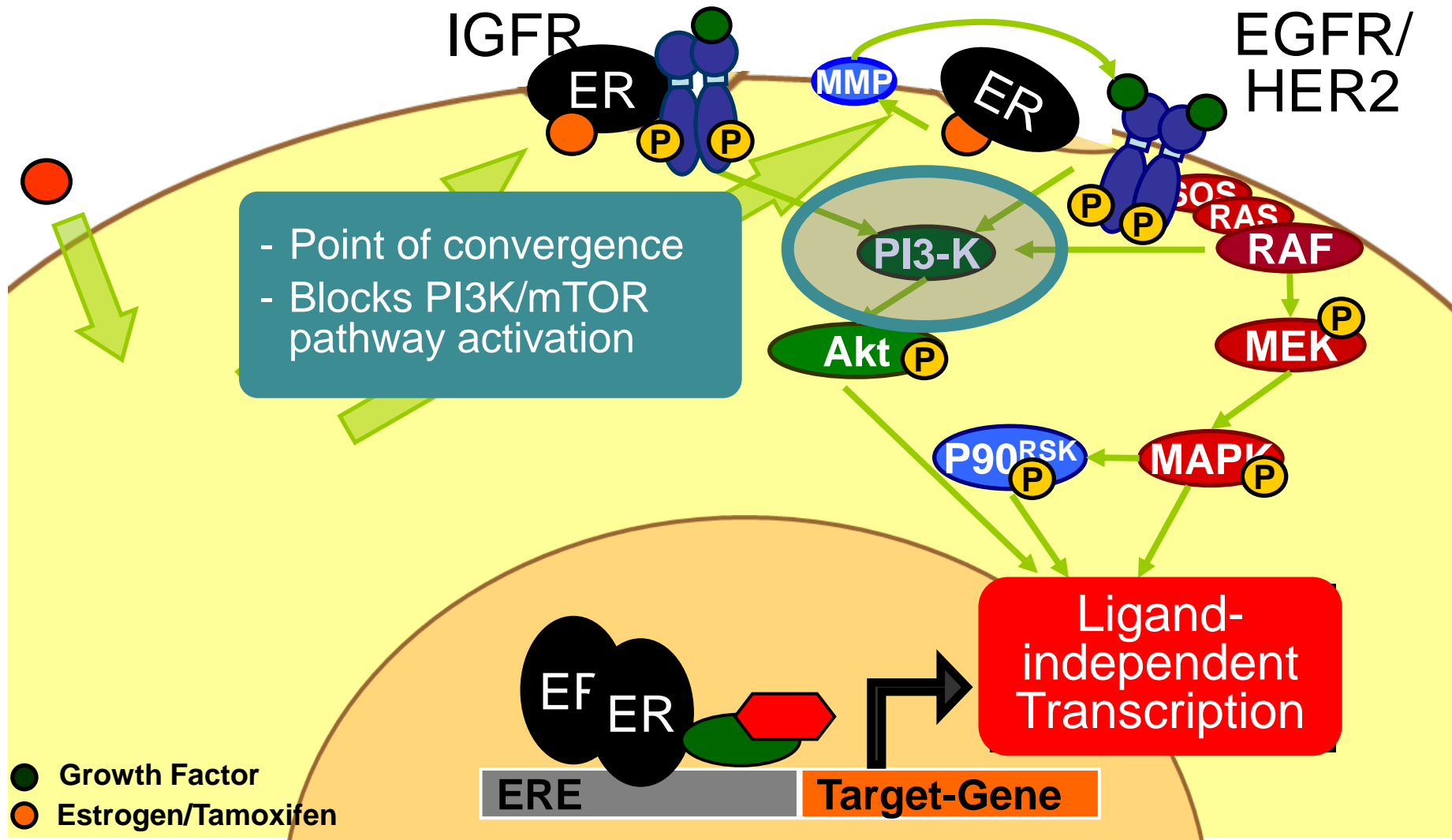
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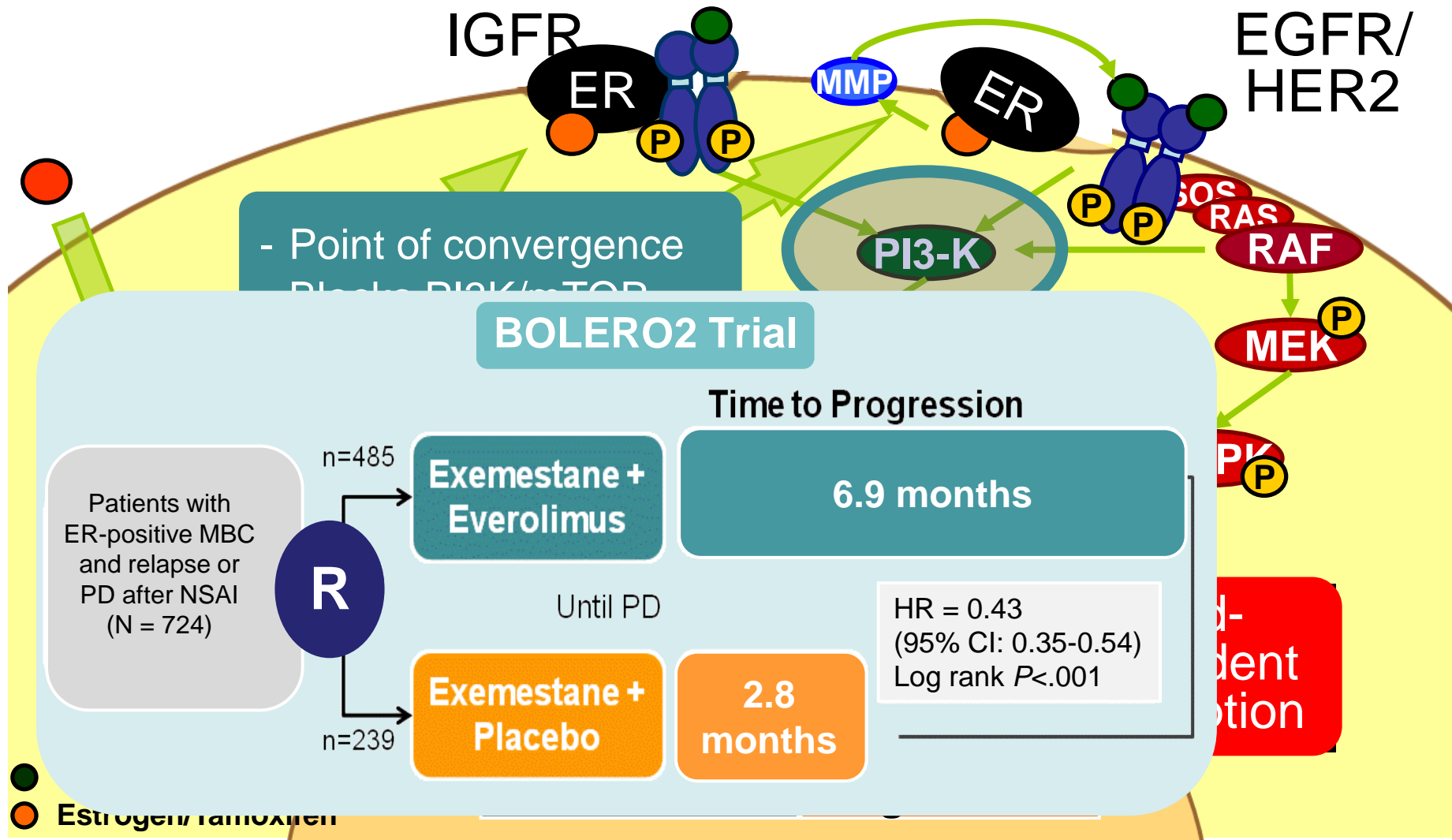
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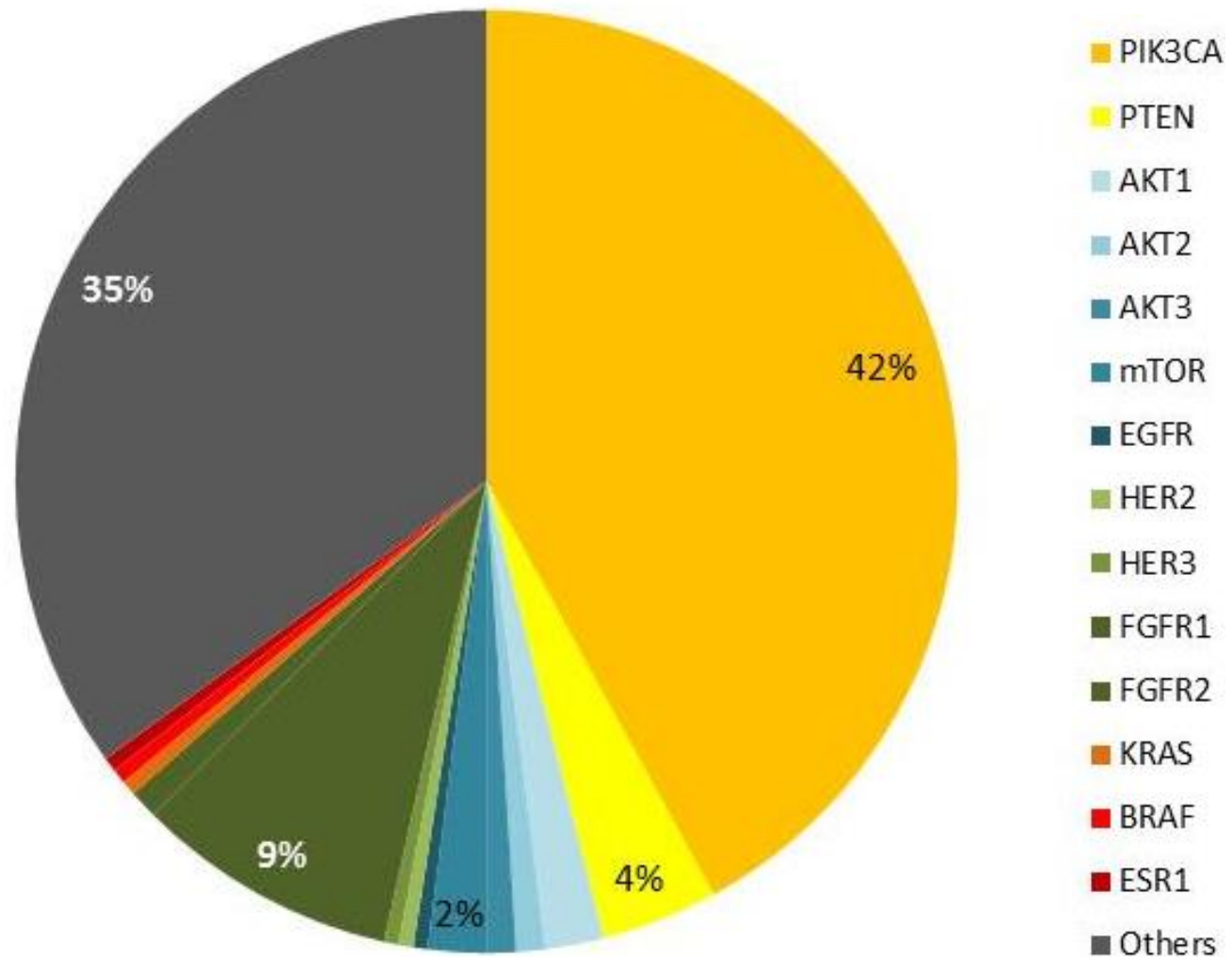
ER-Signaling and Anti-oestrogen Therapy

Understanding the Cellular Signaling Network



Genetic Aberrations in Signaling Pathways in Luminal Tumors

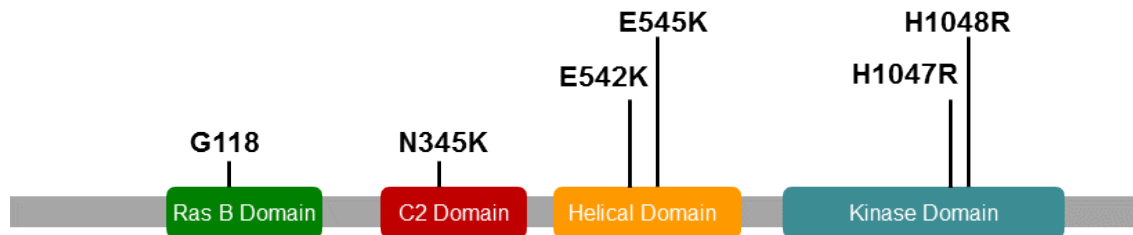
Target-Focused Classification



Genetic Aberrations in Signaling Pathways in Luminal Tumors

Target-Focused Classification

PIK3CA Mutations in Breast cancer



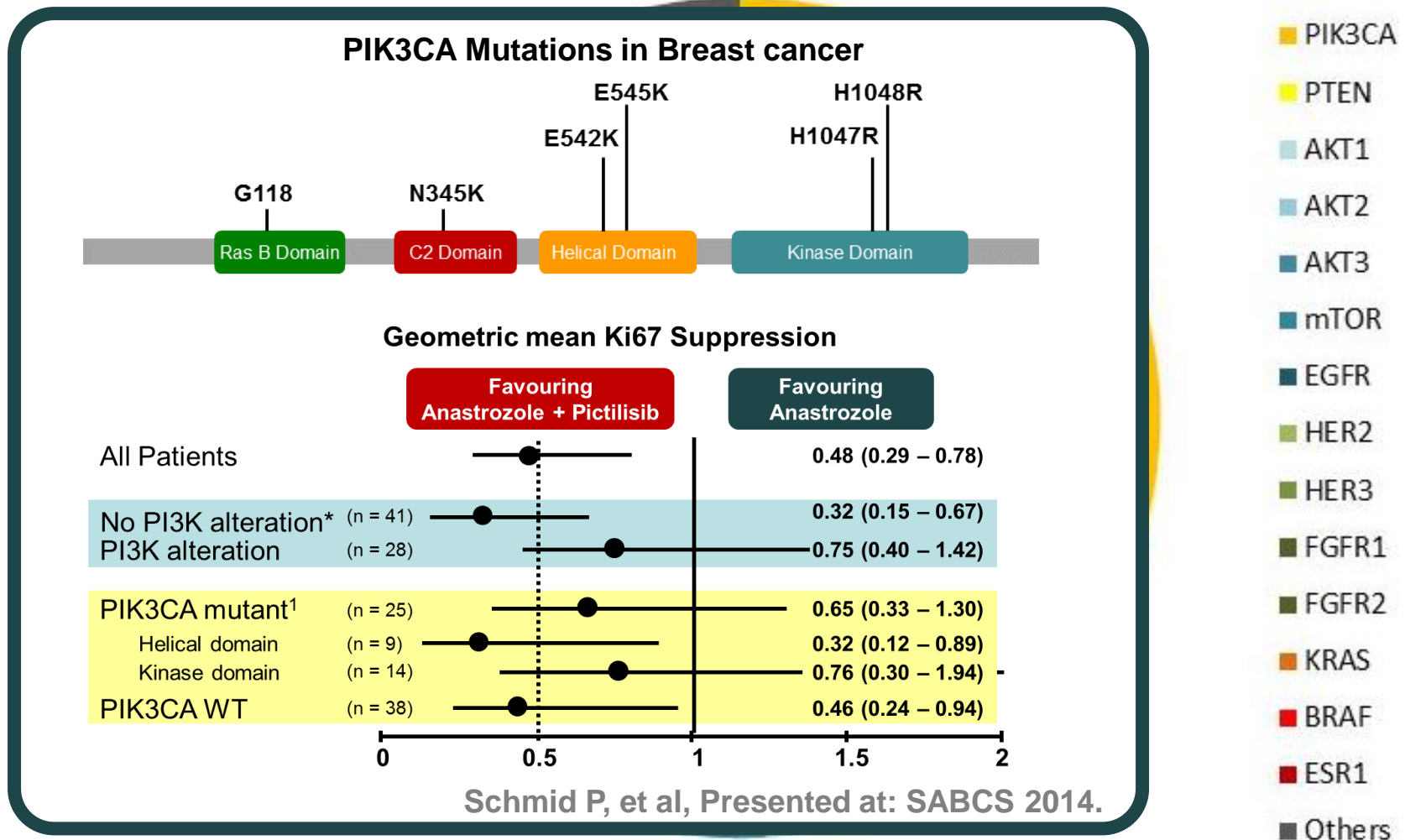
- **Activating PI3KCa mutations occur in 30-40% of ER+ BC**
- **Are PIK3CA the best biomarker for benefit from PI3K/mTOR inhibition?**

Schmid P, et al, Presented at: SABCS 2014.

- PIK3CA
- PTEN
- AKT1
- AKT2
- AKT3
- mTOR
- EGFR
- HER2
- HER3
- FGFR1
- FGFR2
- KRAS
- BRAF
- ESR1
- Others

Genetic Aberrations in Signaling Pathways in Luminal Tumors

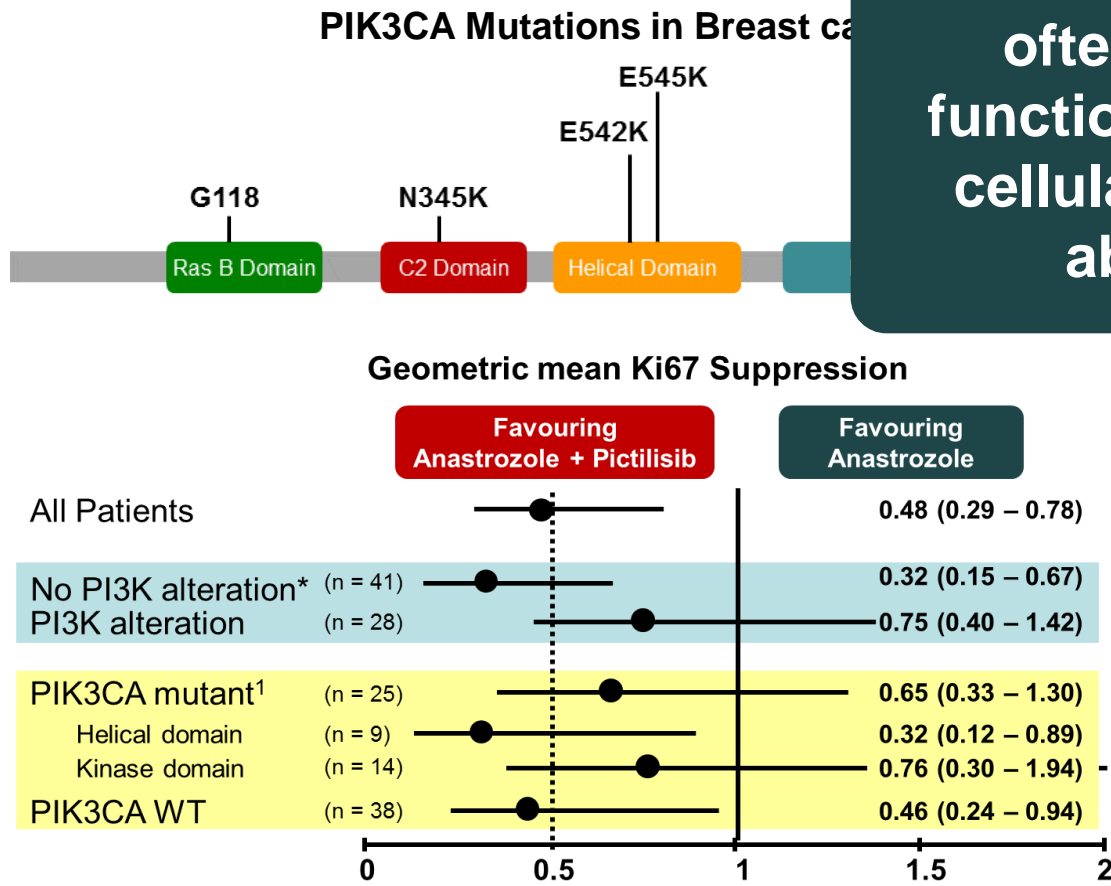
Target-Focused Classification



Genetic Aberrations in Signaling Pathways in Luminal Tumors

Target-Focused Classification

Isolated genetic analysis often fails to define functional relevance and cellular dependence of aberrant target

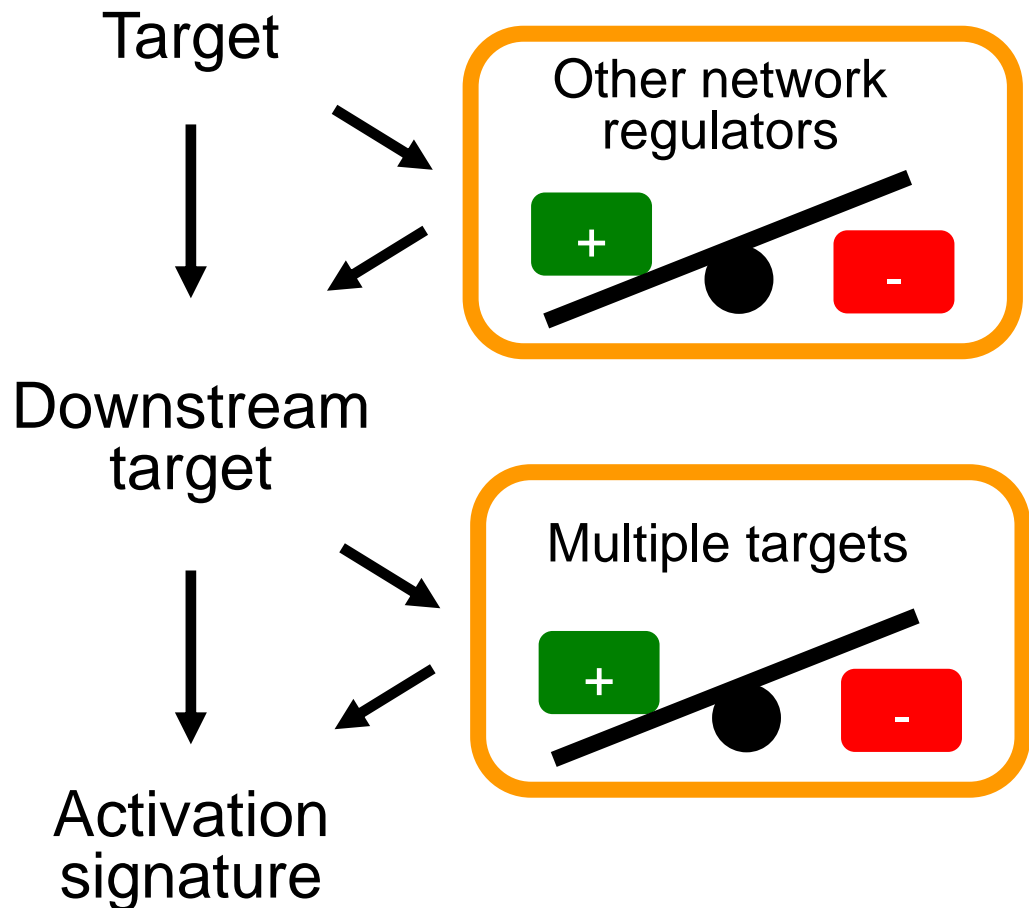


Schmid P, et al, Presented at: SABCS 2014.

- mTOR
- EGFR
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- Others

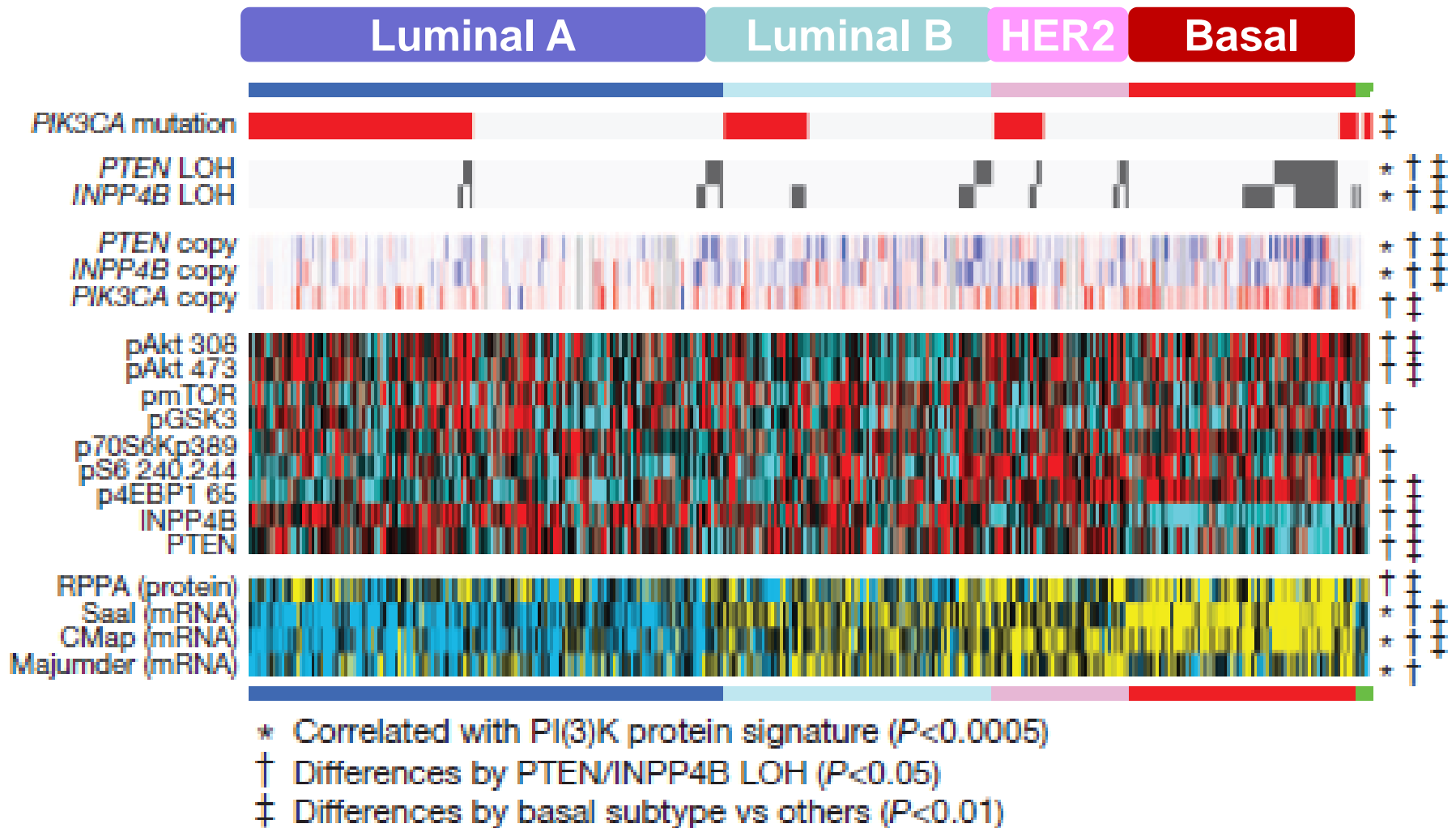
Understanding Cellular Signaling Networks: PI3K/mTOR Pathway

Challenges Around Identifying Biomarkers



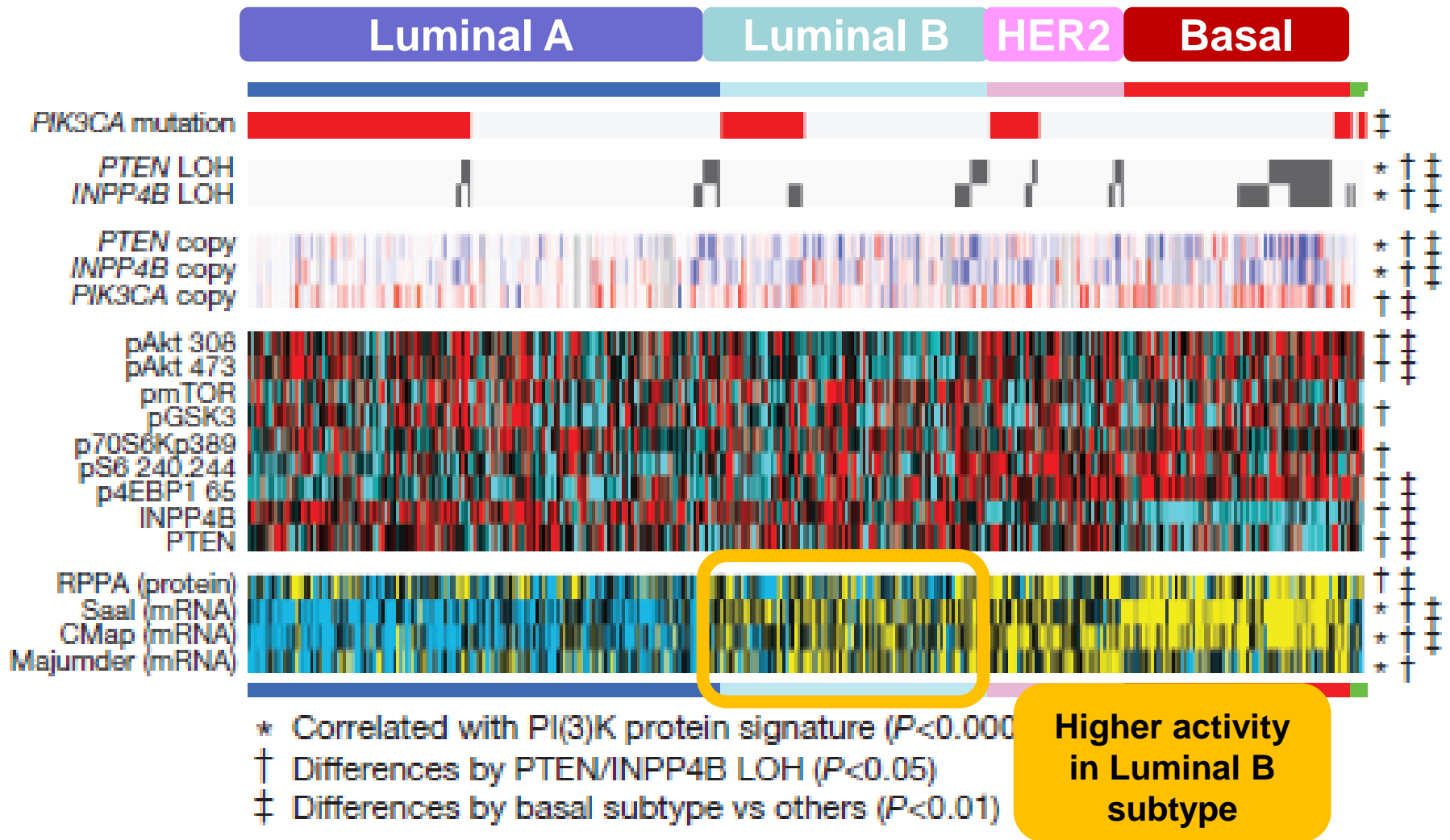
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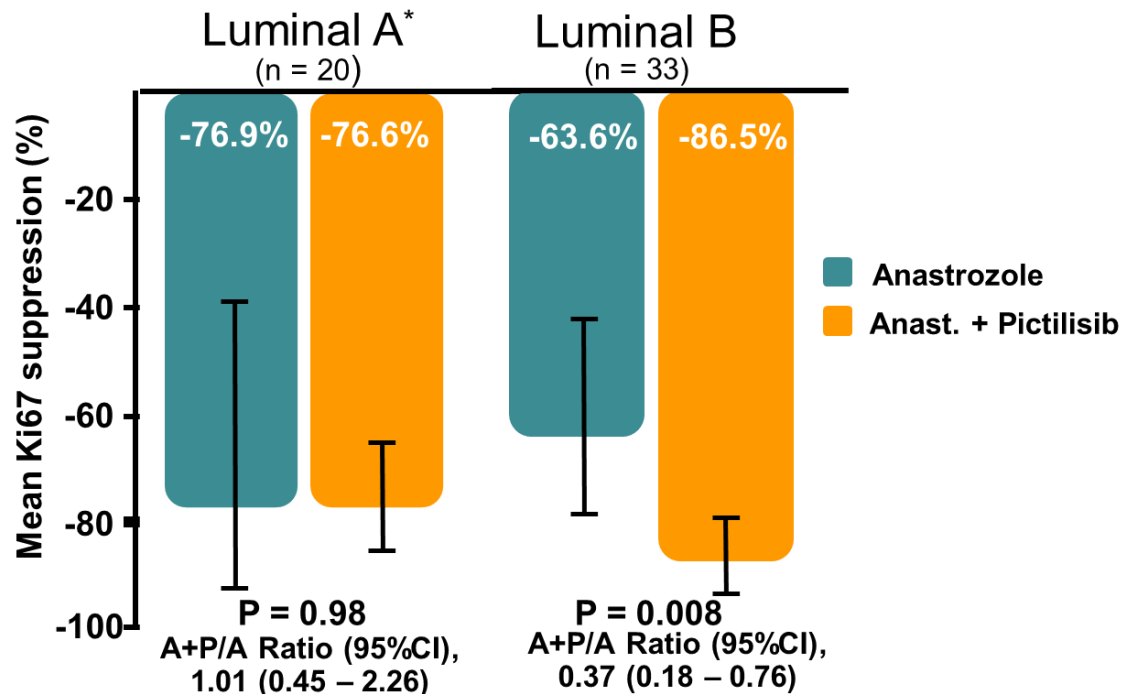
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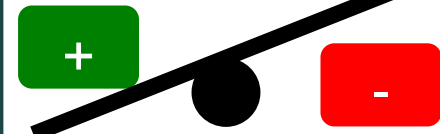
Challenges Around Identifying Biomarkers

Geometric mean Ki67 Suppression by Subtype



Schmid P et al, SABCS 2014

Other network regulators



Multiple targets

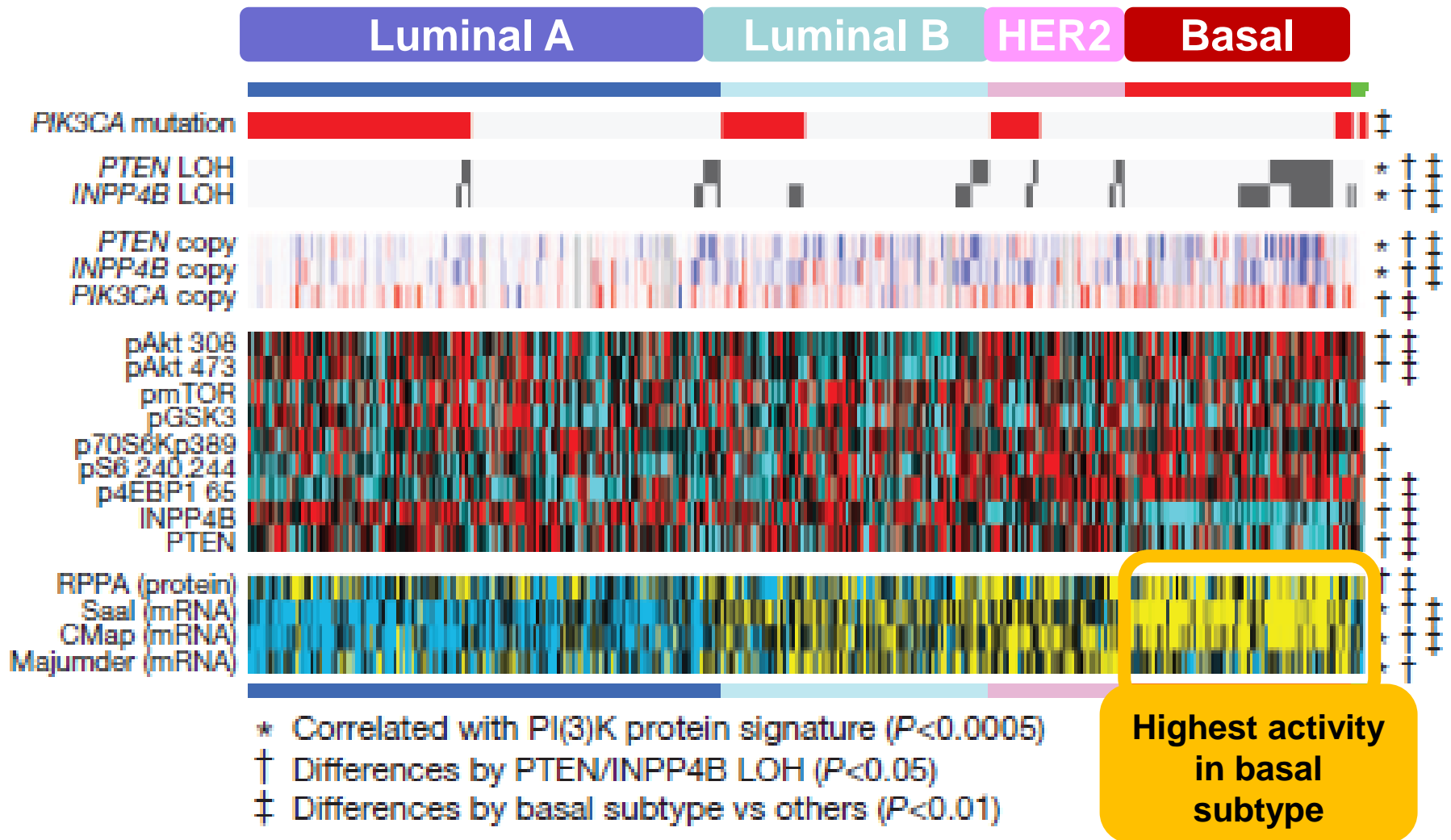


Highest activity
in basal
subtype

signature

Understanding Cellular Signaling Networks: PI3K/mTOR Pathway

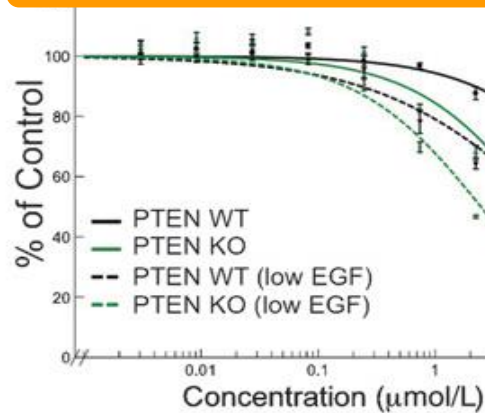
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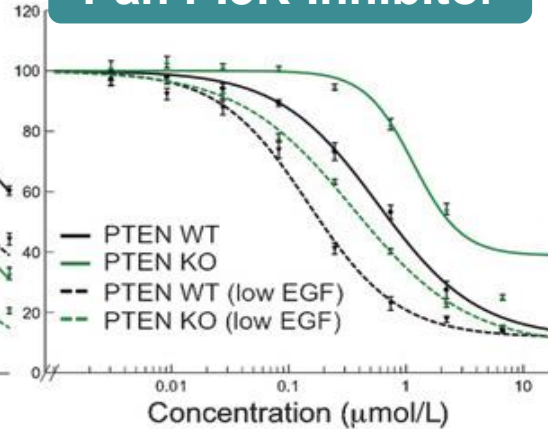
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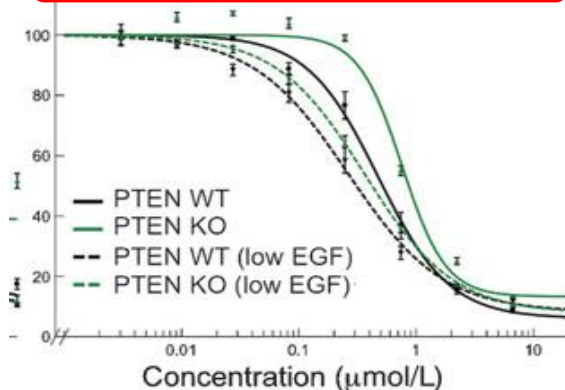
AKT-Inhibitor



Pan PI3K-Inhibitor



PI3K/mTOR-Inhibitor



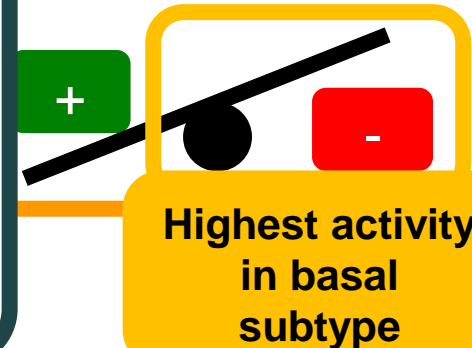
Cancer with PTEN loss may be particularly sensitive to AKT inhibitors

Lin J, et al. *Clin Cancer Res.* 2013;19(7):1760-1772.

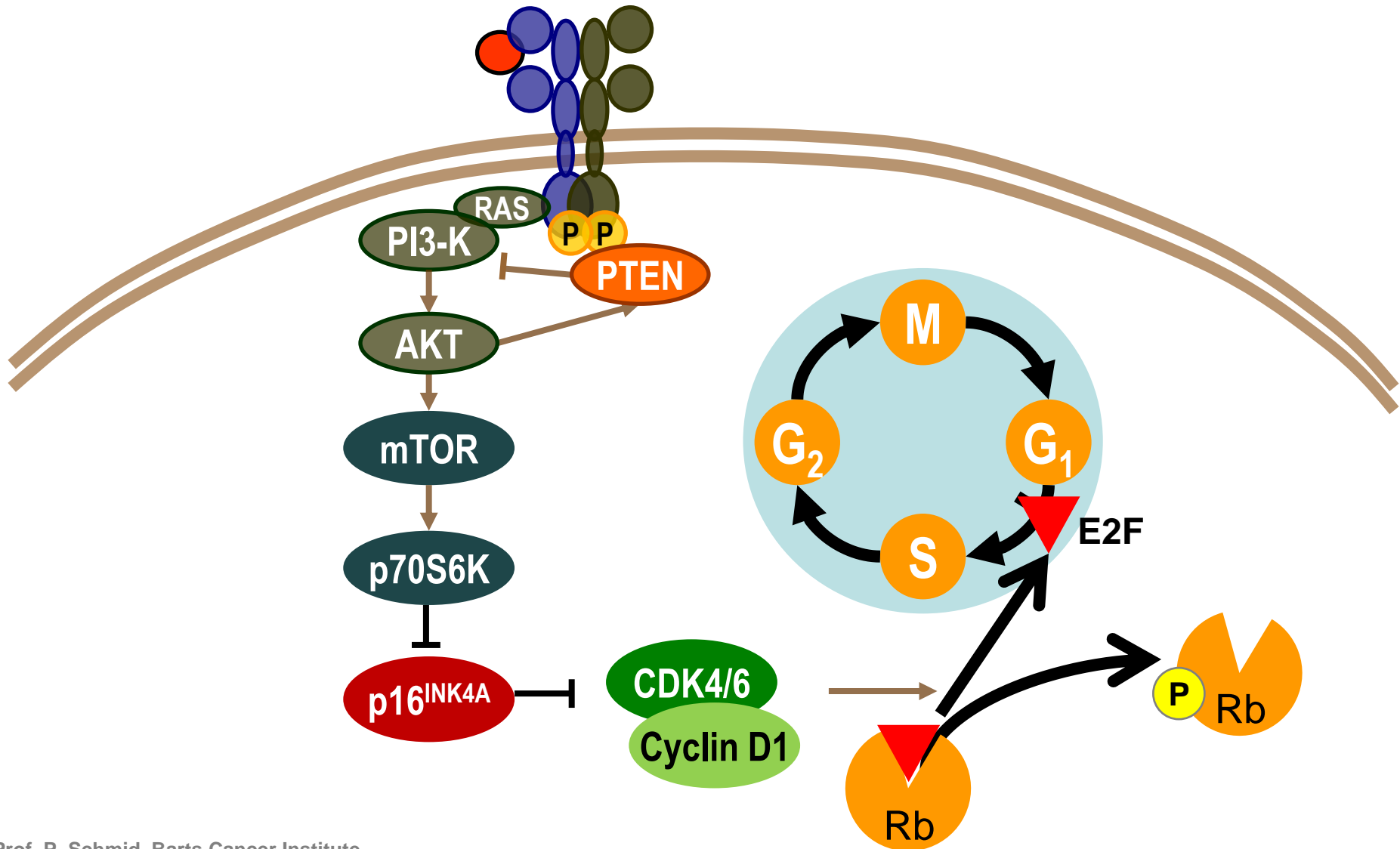
Other network regulators



Multiple targets



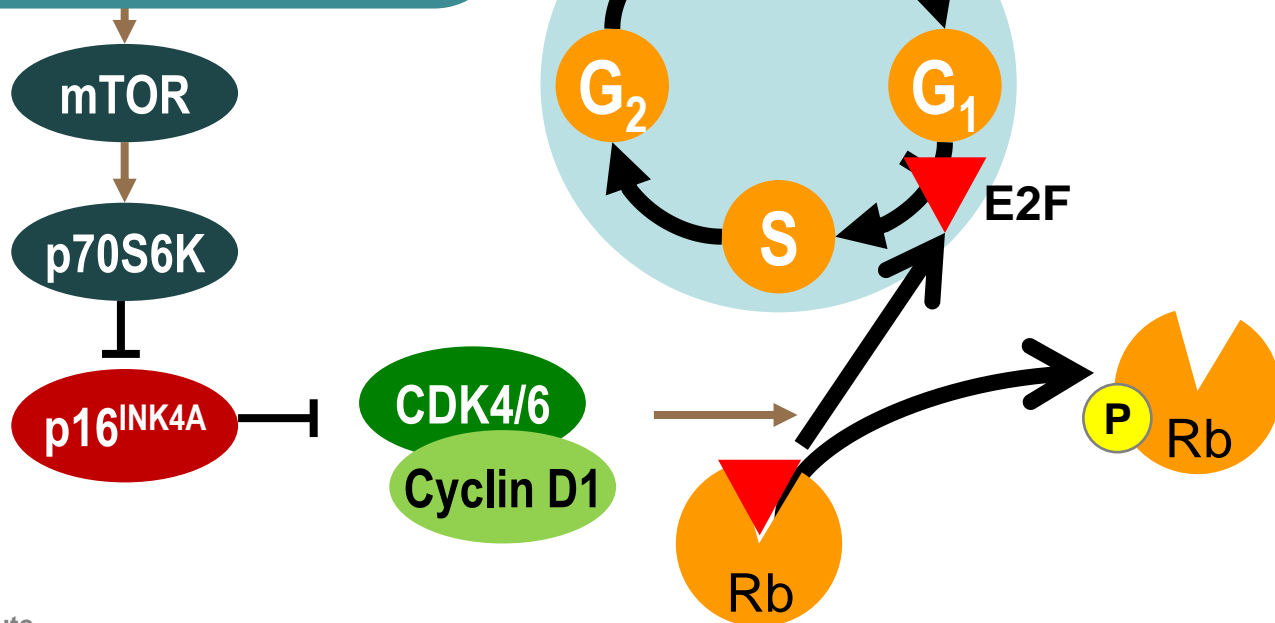
Targeting Cell Cycle Control (CDK4/6)



Targeting Cell Cycle Control (CDK4/6)

Targeting CDK4/6:

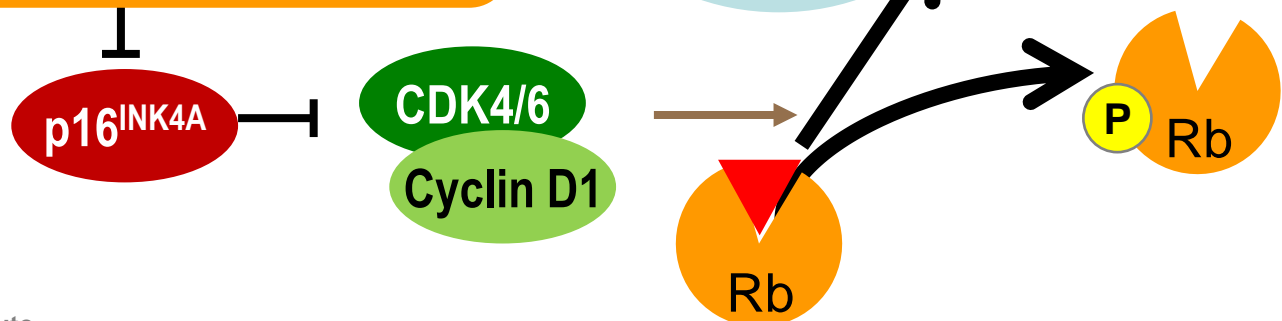
- Intact Rb required for therapeutic approach
- CyclinD-CDK4/6 axis frequently dysregulated in ER+ BC with intact Rb (LumA 23%, LumB 49%)
- Loss of Rb common in TNBC



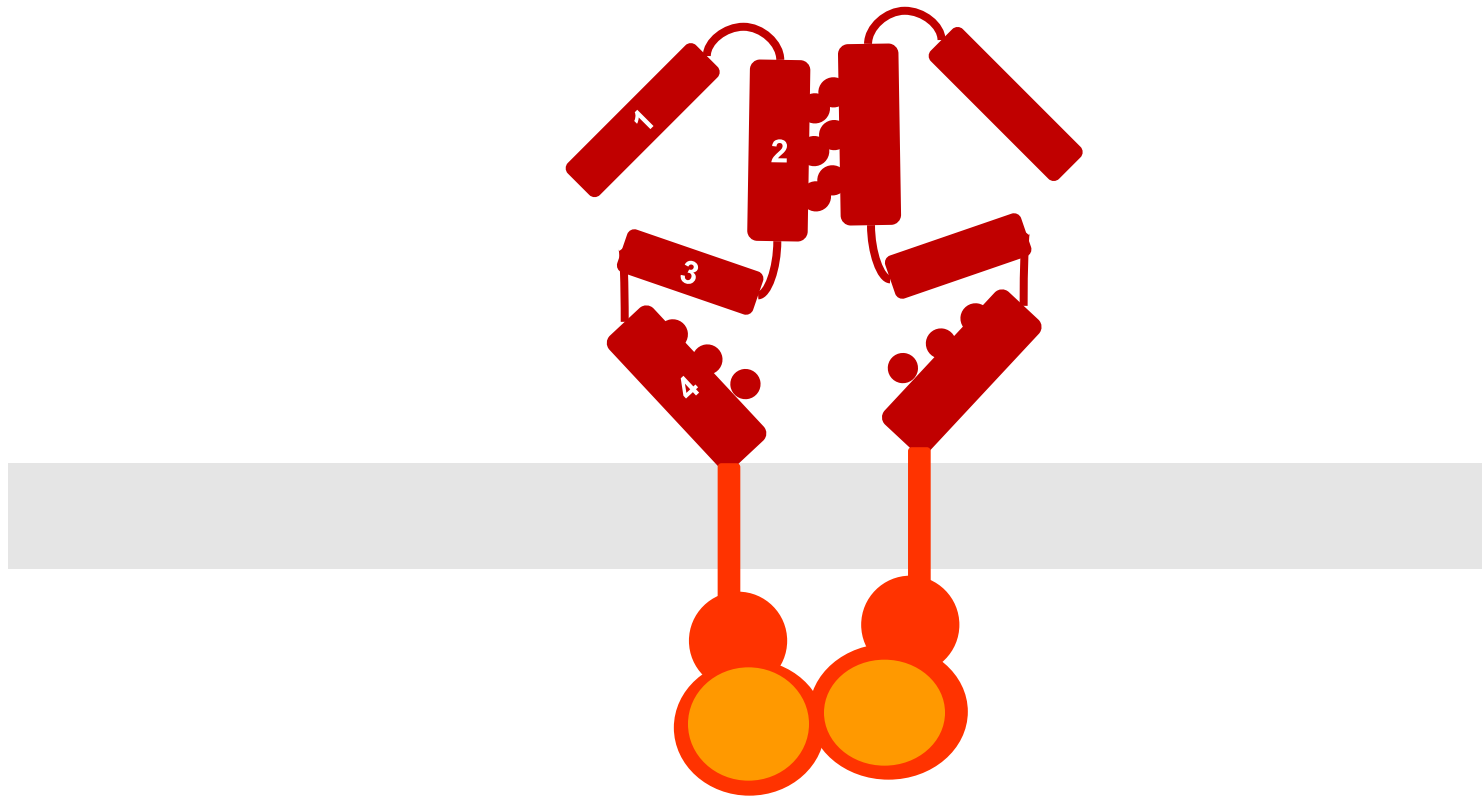
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Targeting CDK4/6:

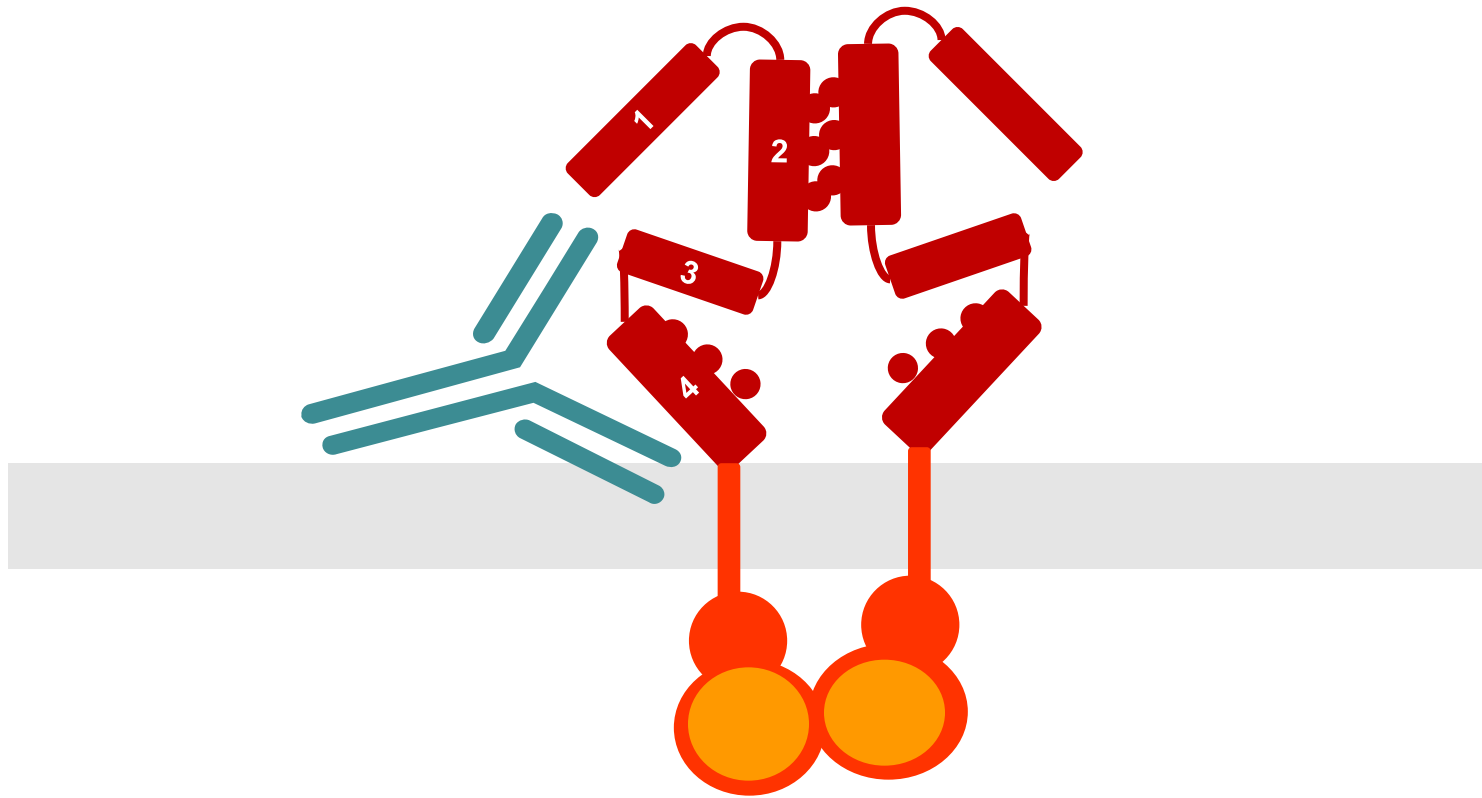
- Intact Rb required for therapeutic approach
 - CyclinD-CDK4/6 axis frequently dysregulated in ER+ BC with intact Rb (LumA 23%, LumB 49%)
 - Loss of Rb common in TNBC
- Early studies suggest substantial benefit in ER+ disease
 - Cyclin D-CDK4/6 aberrations are not predictive of response



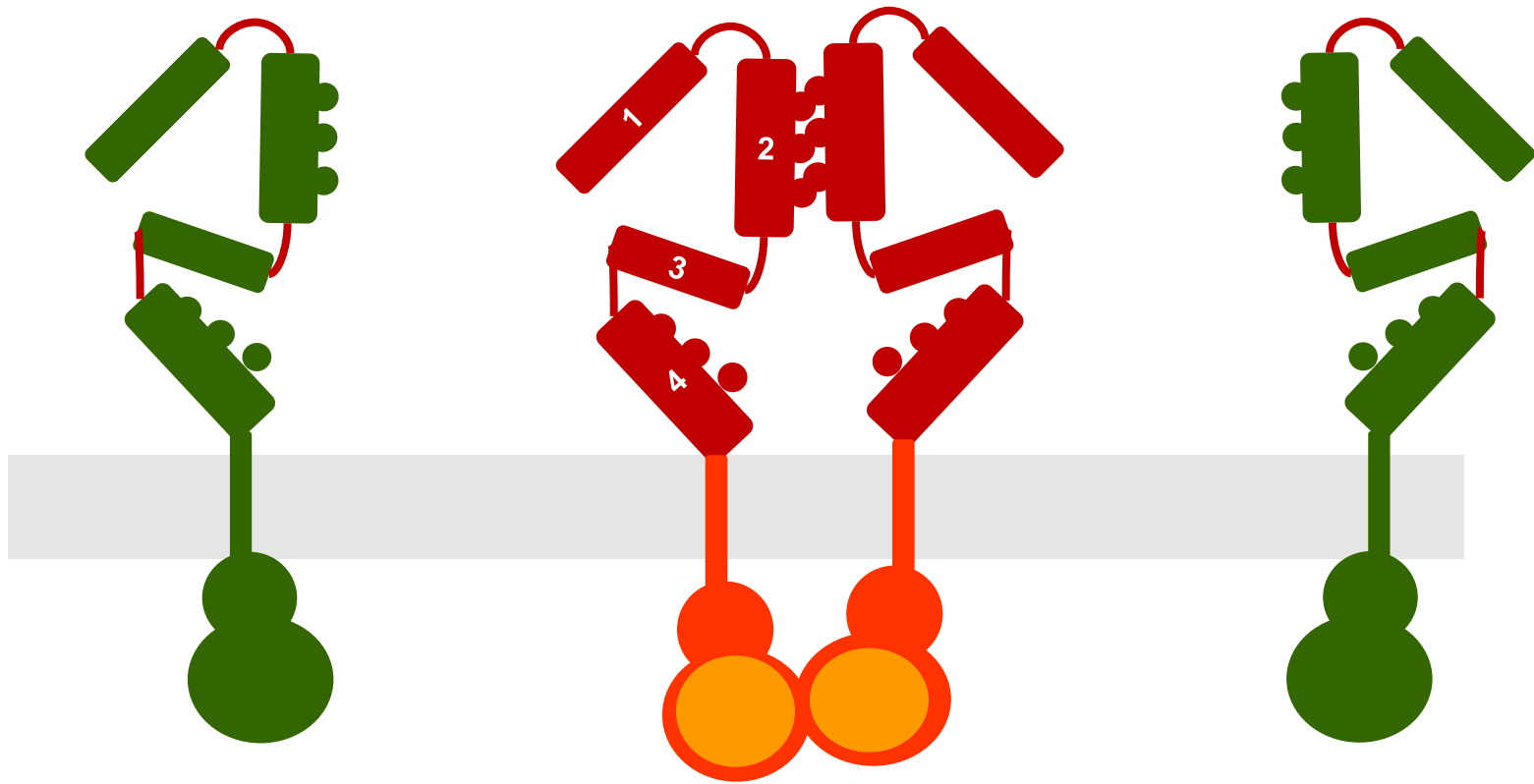
Targeting HER2+ Disease



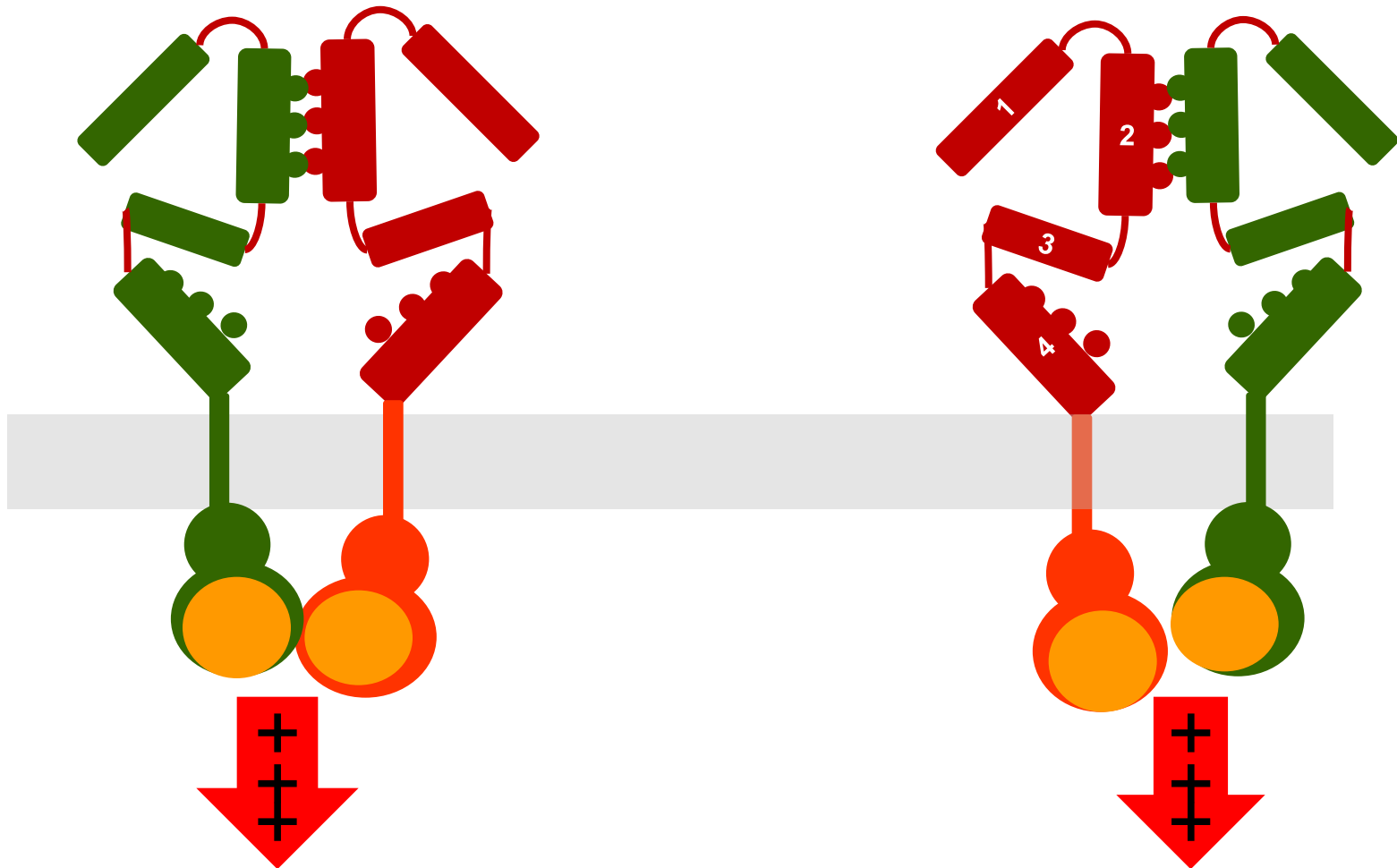
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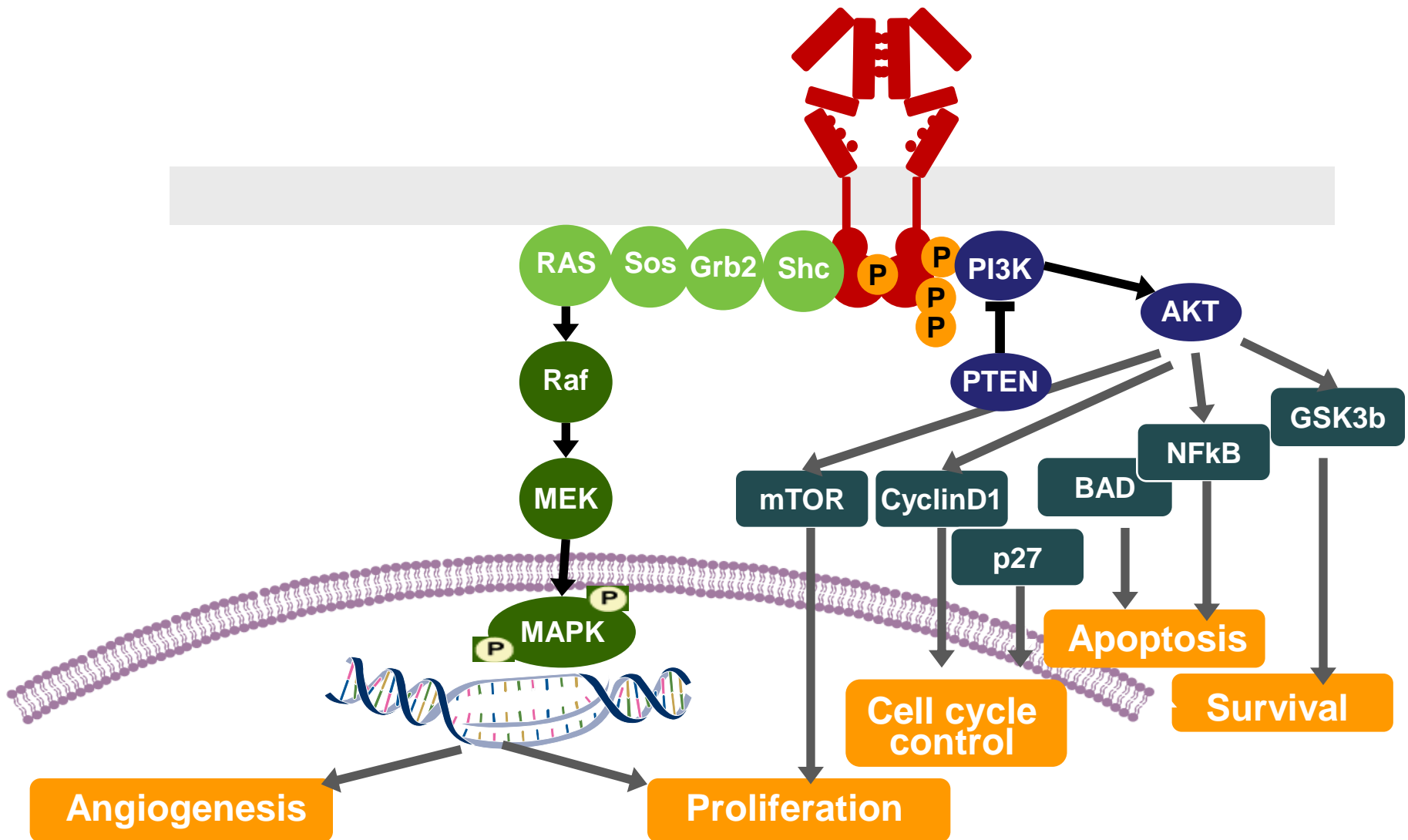


Targeting HER2+ Disease



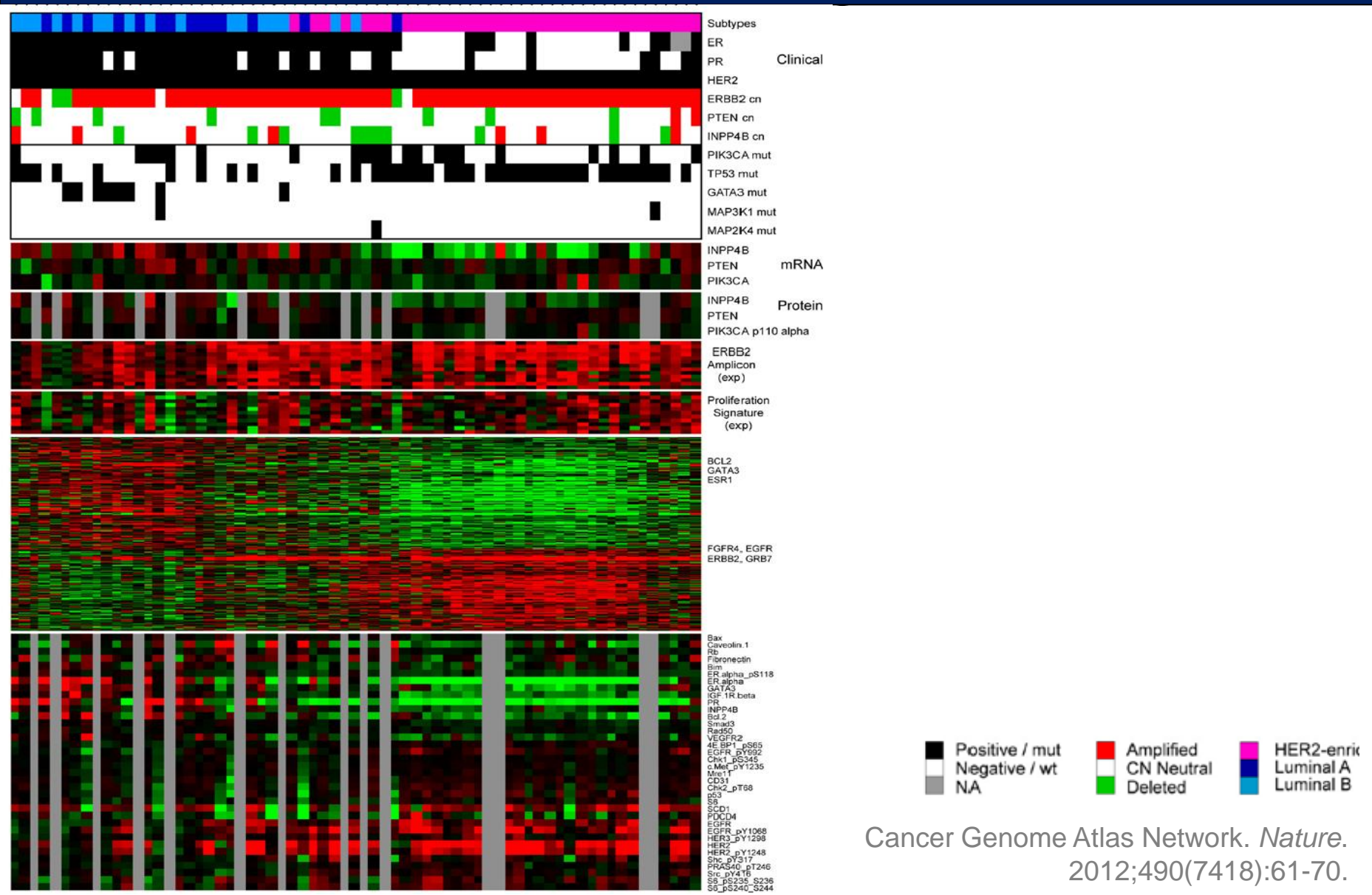
Targeting HER2+ Disease

Intracellular Signaling Network



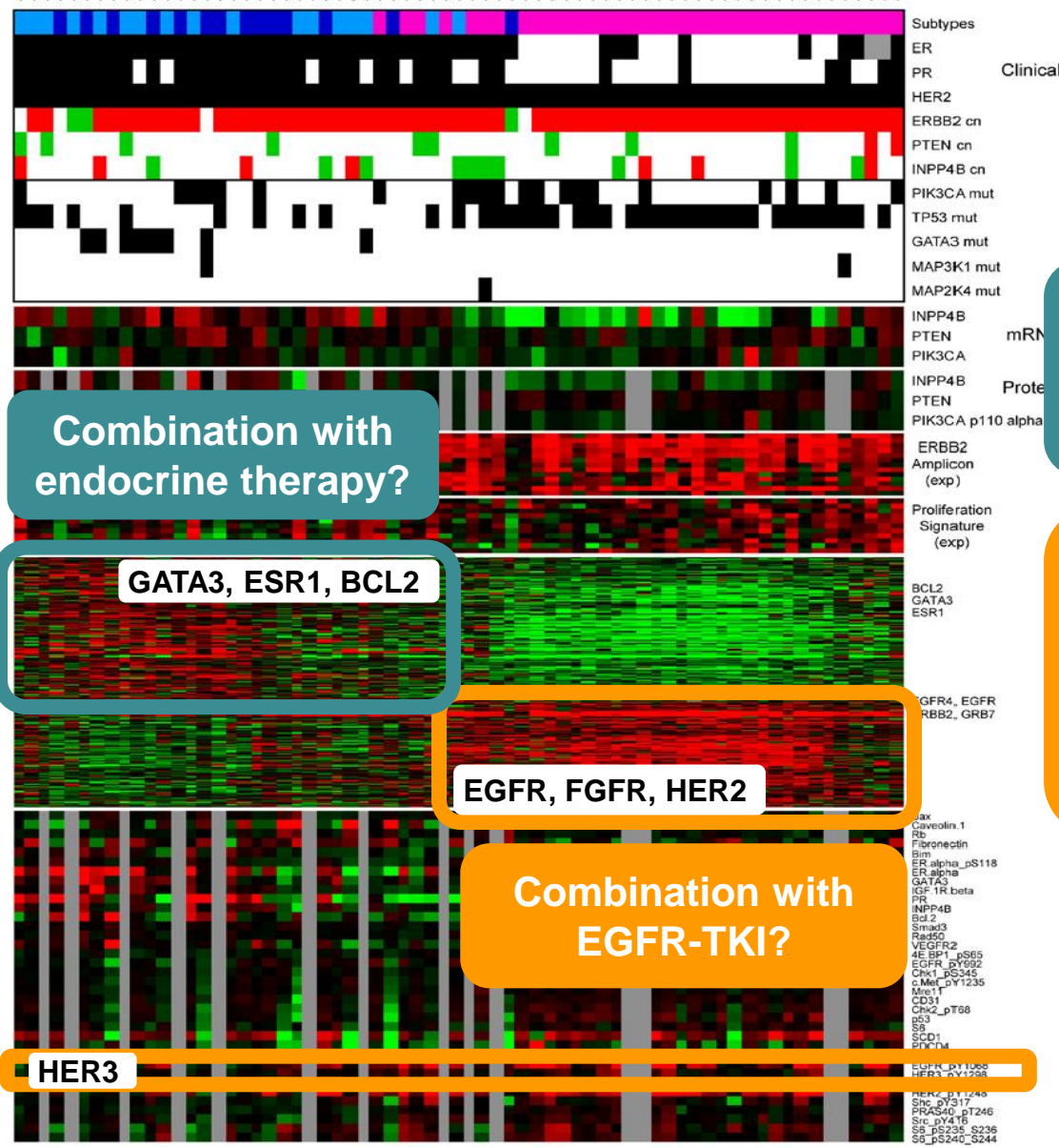
Targeting HER2+ Disease

Luminal vs HER2 Subtype & Potential Co-Targets



Targeting HER2+ Disease

Luminal vs HER2 Subtype & Potential Co-Targets



Combination with endocrine therapy?

GATA3, ESR1, BCL2

EGFR, FGFR, HER2

Combination with EGFR-TKI?

HER3

HER2+/Luminal:

- Strong signal for luminal cluster GATA3, BCL2, ESR1

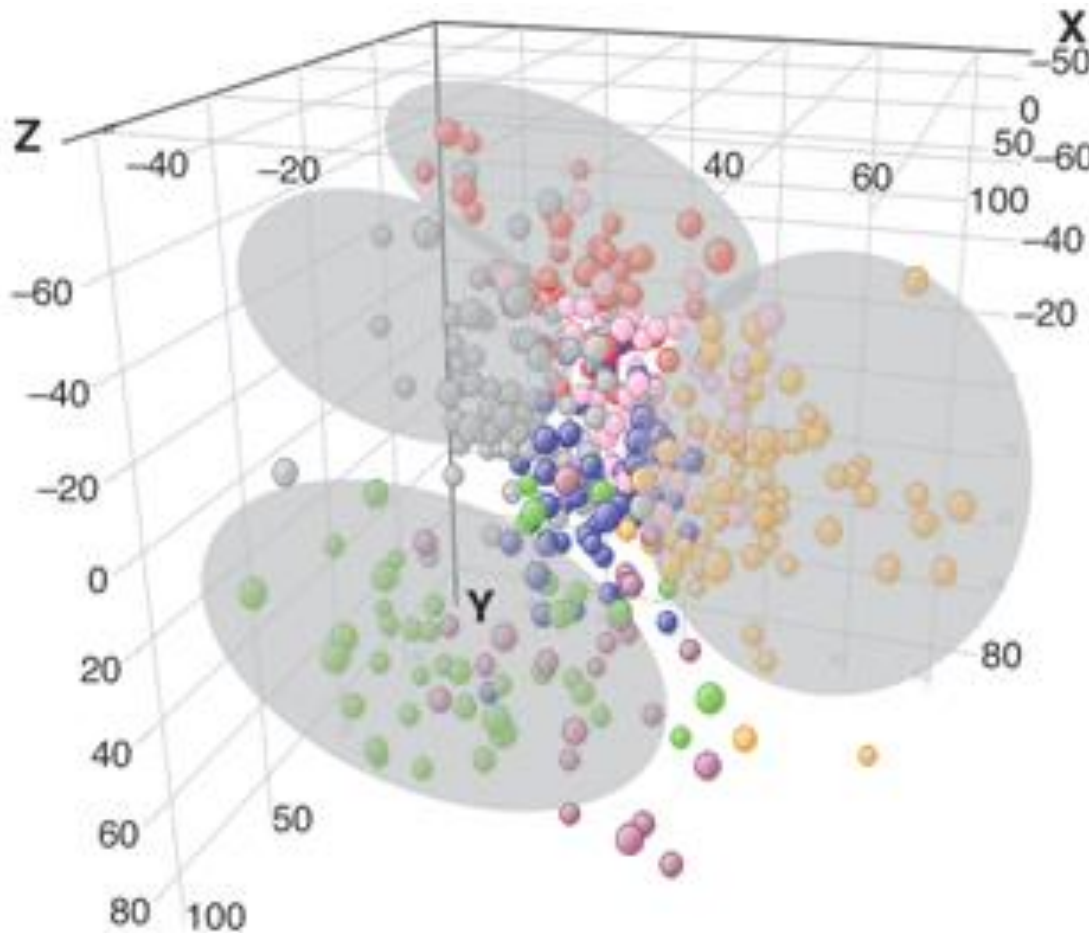
HER2+/HER2E :

- Strong signal for EGFR, FGFR4, HER2 amplicon, pS6;
- Amplification of CDK4, cyclin D1, EGFR, FGFRs



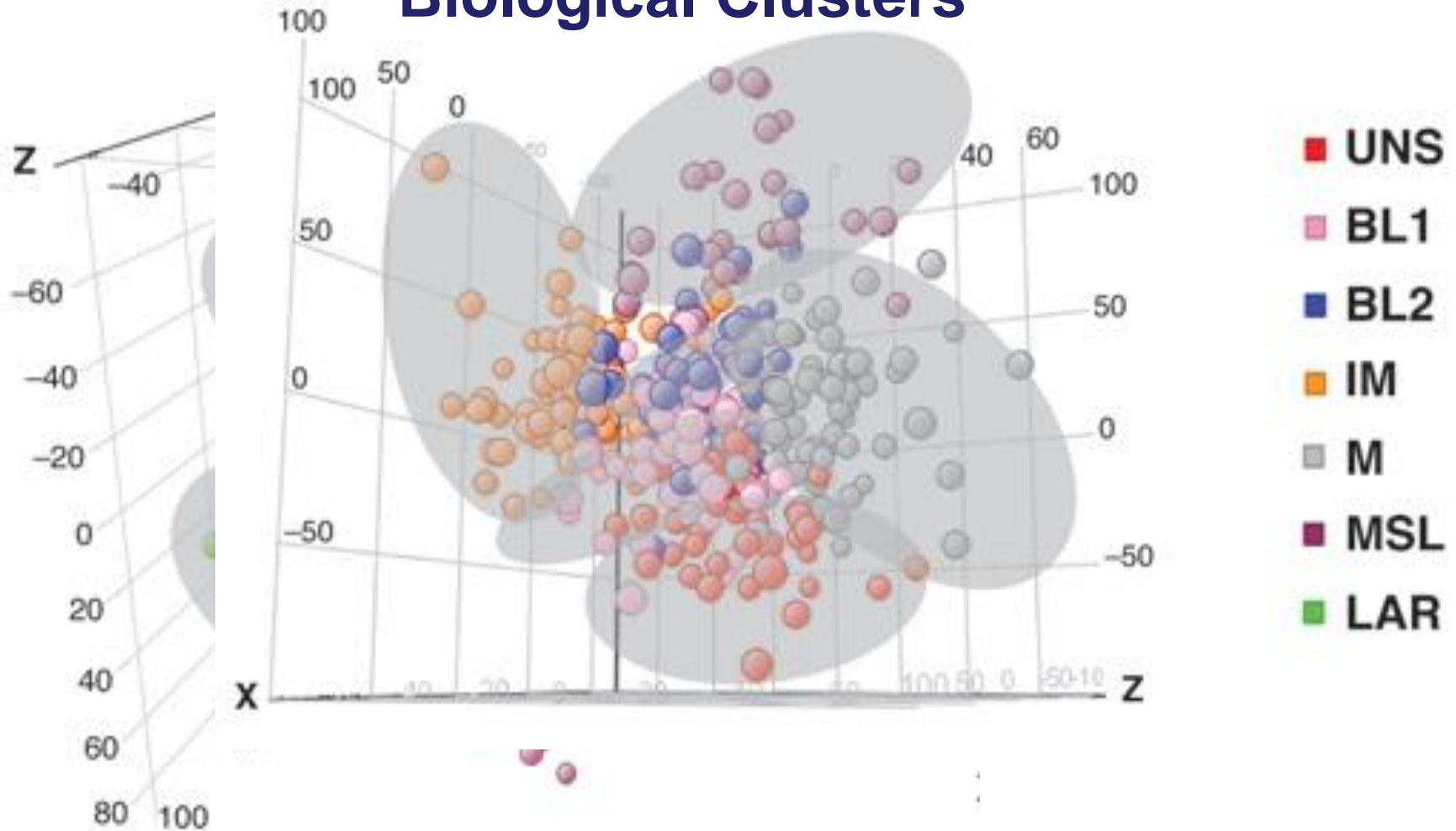
Triple Negative Cancer: Potential Treatment Targets? Heterogeneity Requires Different Strategies

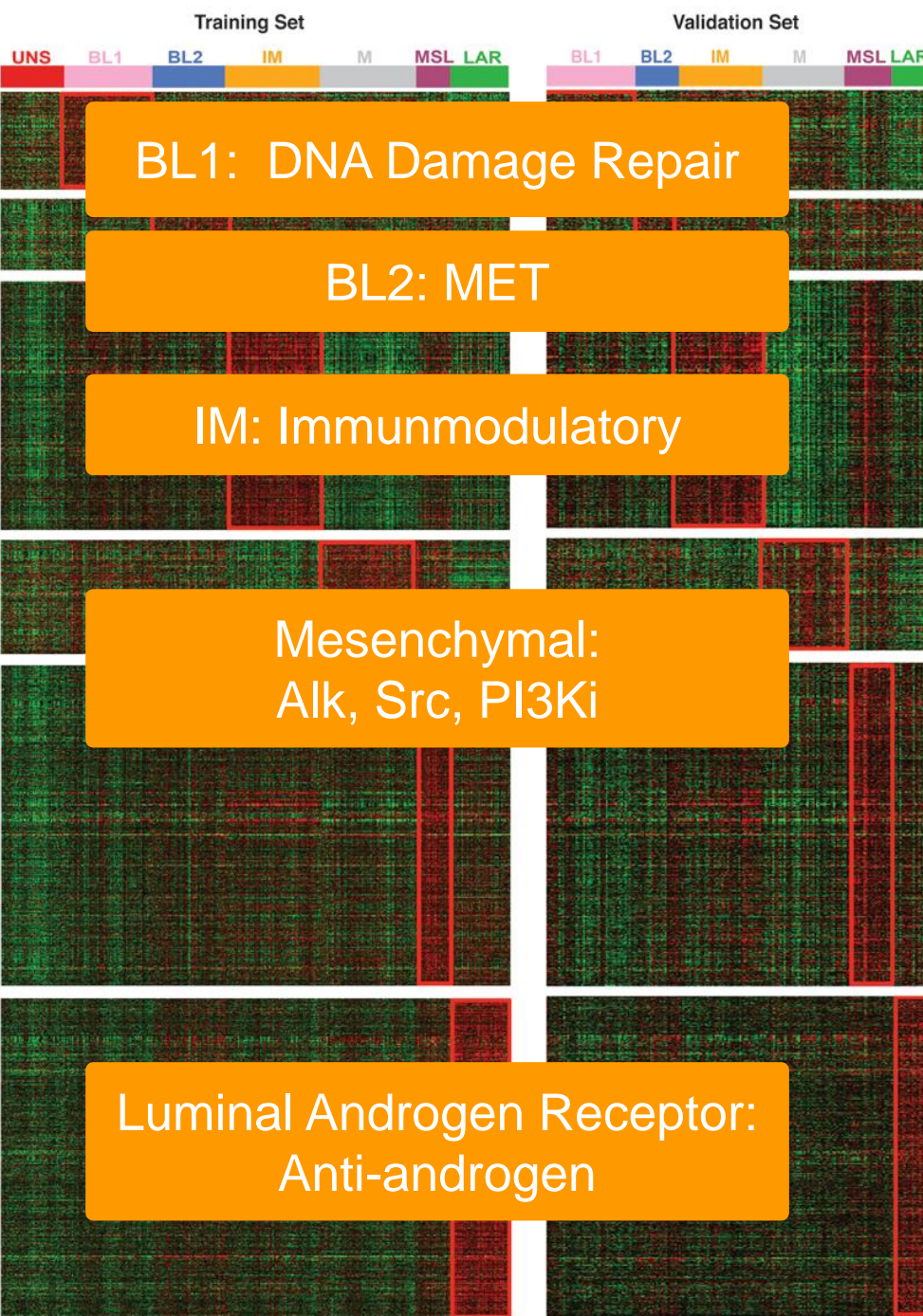
Biological Clusters



Triple Negative Cancer: Potential Treatment Targets? Heterogeneity Requires Different Strategies

Biological Clusters





GO Terms/ Canonical Pathways

Basal-like 1

Cell Cycle
DNA Replication Reactome
G₁ Pathway
RNA Polymerase
ATR/ BRCA Pathway
G₁ to S Cell Cycle

Basal-like 2

EGF Pathway
NGF Pathway
MET Pathway
WNT β -catenin Pathway
IGF1R Pathway
Glycolysis/ Gluconeogenesis

Immunomodulatory

CTLA4 Pathway
IL12 Pathway
NK Cell Pathway
Th1/Th2 Pathway
IL7 Pathway
Antigen Processing/ Presentation
NFKB Pathway
TNF Pathway
T Cell Signal Transduction
DC Pathway
BCR Signaling Pathway
NK Cell Mediated Cytotoxicity
JAK/ STAT Signaling Pathway
ATR/ BRCA Pathway

Mesenchymal-like

IGF/ mTOR Pathway
ECM Pathway
Regulation of Actin by RHO
WNT Pathway
ALK Pathway
TGF β Pathway

Mesenchymal Stem-like

ECM Receptor Interaction
TOR Pathway
WNT β -catenin
Focal Adhesion
Inositol Phosphate Metabolism
NFKB Pathway
EGF Pathway
ALK Pathway
GH Pathway
NK Cell Mediated Toxicity
RAC1 Pathway
GPCR Pathway
ERK1/2 Pathway
Integrin Mediated Adhesion
ABC Transporters General
RHO Pathway
Smooth Muscle Contraction
Calcium Signaling Pathway
Adipocytokine Signaling Pathway
PDGF Pathway
TGF β Pathway

Luminal AR

Pentose/Glucuronate Interconversion
Glutathione Metabolism
Tyrosine Metabolism
Steroid Biosynthesis
Porphyrin Metabolism
Androgen and Estrogen Metabolism
Glycosphingolipid Metabolism
Flagellar Assembly
Citrate Cycle TCA
Phenylalanine Metabolism
ATP Synthesis
Starch and Sucrose Metabolism
Arginine and Proline Metabolism
Metabolism by Cytochrome P450
Fructose and Mannose Metabolism
Fatty Acid Metabolism
Alanine and Aspartate Metabolism
Eicosanoid Synthesis
CHREB Pathway
Tryptophan Metabolism



Different Targets for Biological Clusters

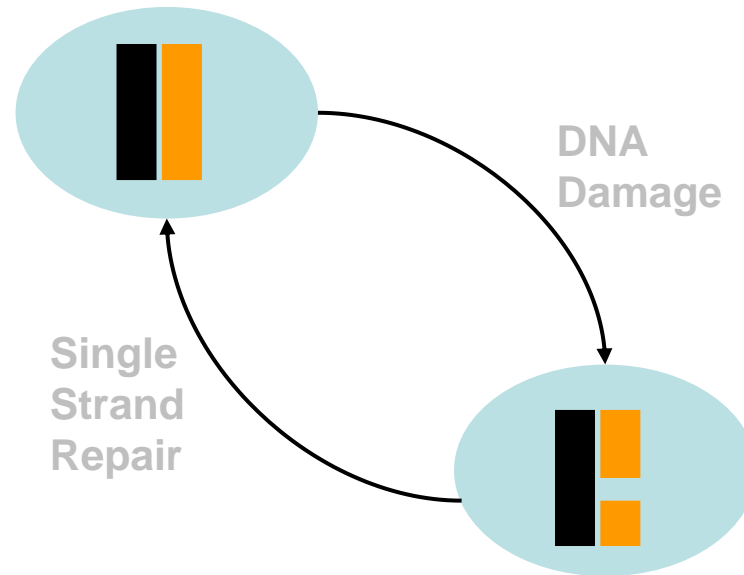
Utilizing Synthetic Lethality Strategies

DNA Damage Repair – BRCA & PARP



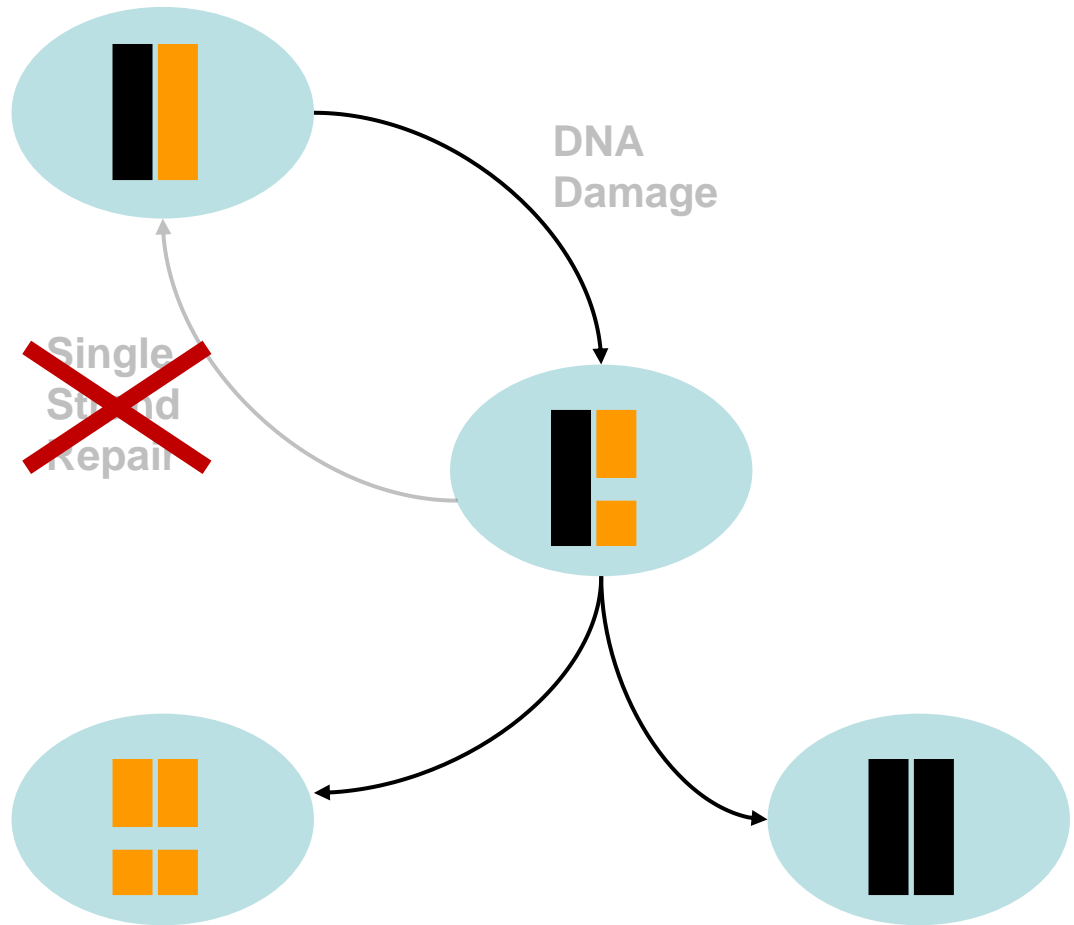
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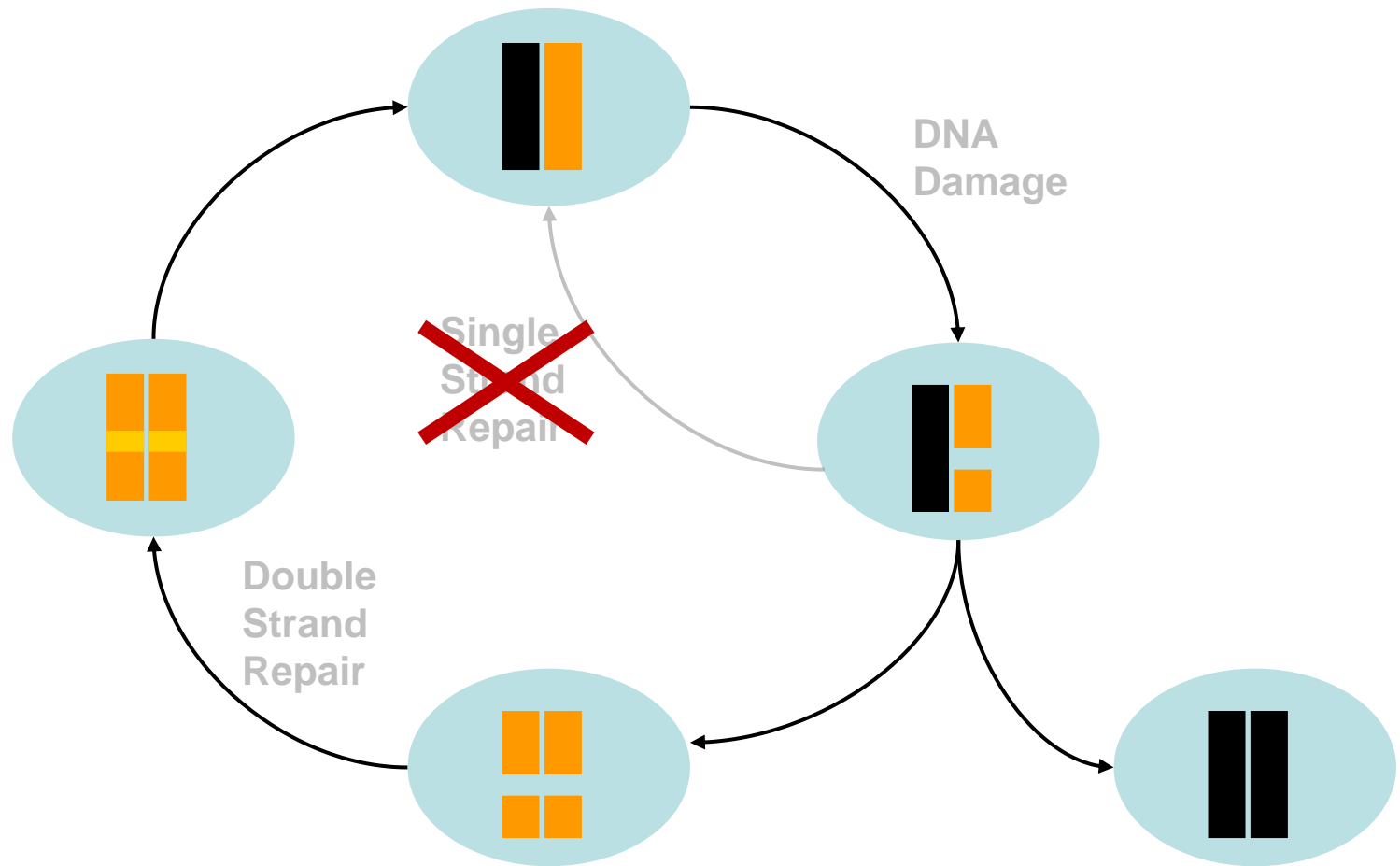
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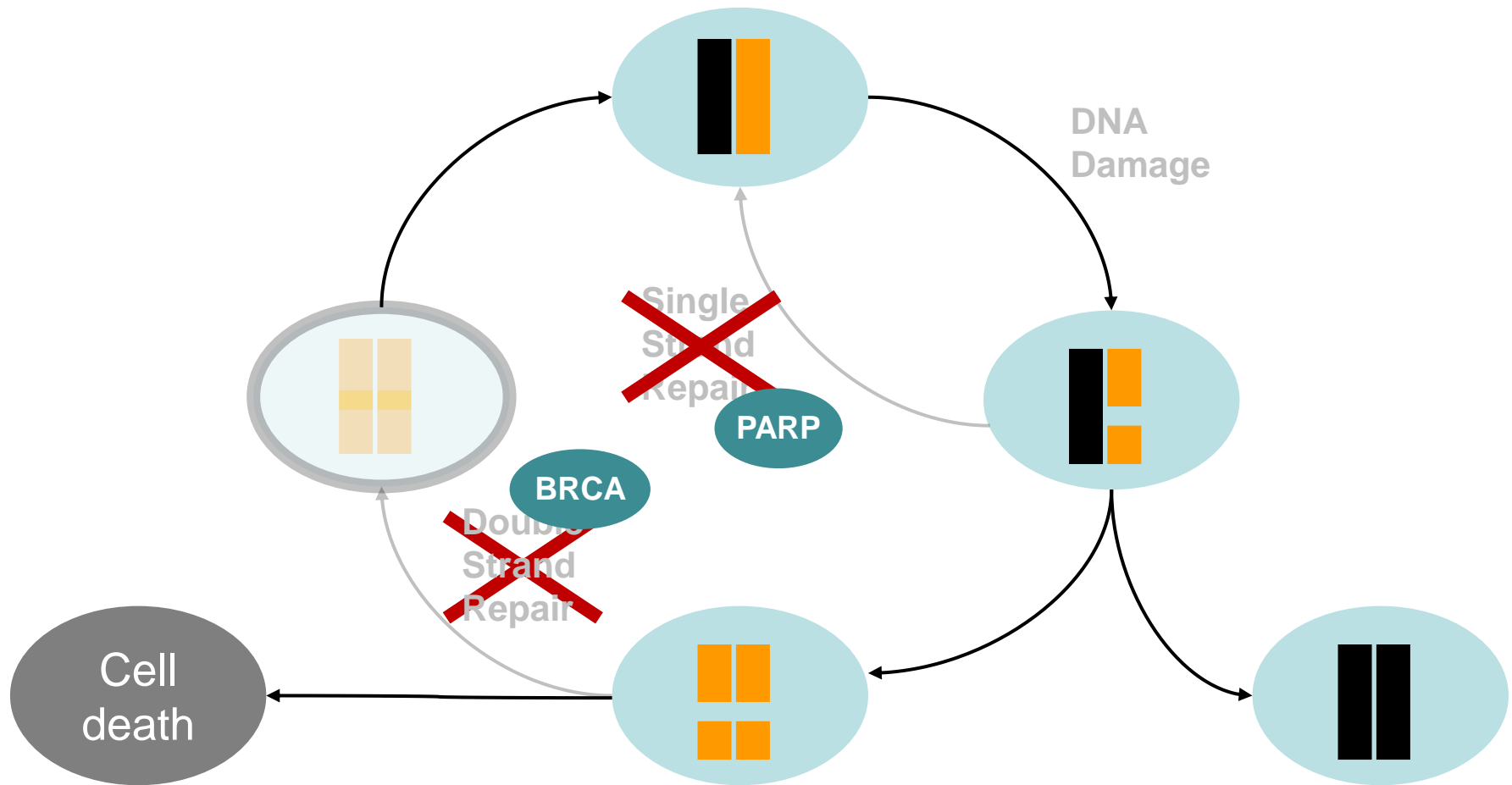
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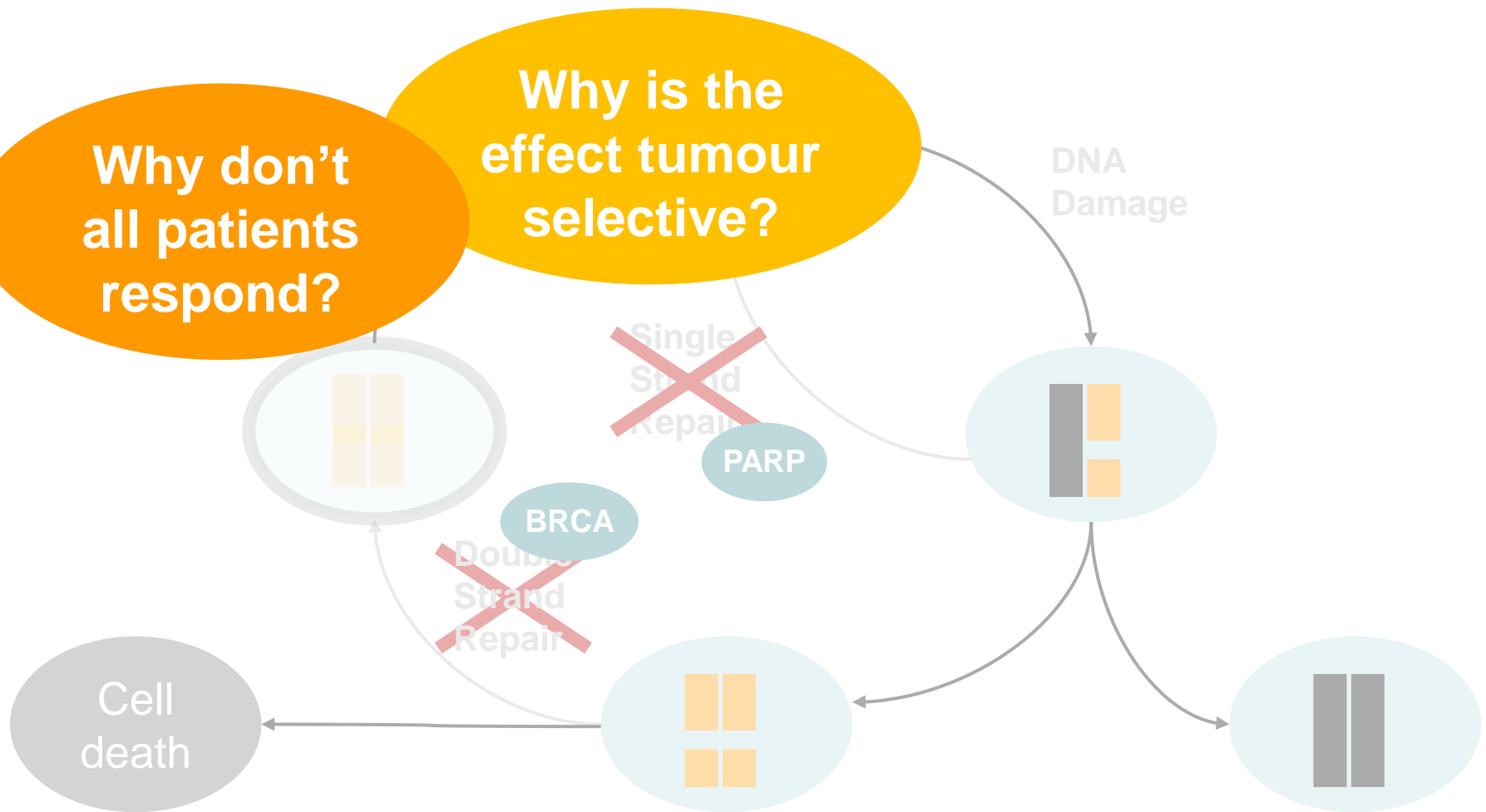


Utilizing Synthetic Lethality Strategies

DNA Damage Repair – BRCA & PARP

Why don't all patients respond?

Why is the effect tumour selective?



Utilizing Synthetic Lethality Strategies

DNA Damage Repair – BRCA & PARP

Why don't all patients respond?

Why is the effect tumour selective?

DNA Damage

Normal Cell

Wild type BRCA2

DNA-binding Domain

BRCA2 del Protein

2500

3418

2002

Functional HR
PARP resistant

Cell death

Tumour Cell

Wild type BRCA2

DNA-binding Domain

BRCA2 del Protein

2500

3418

2002

Inactive HR
PARP sensitive

Utilizing Synthetic Lethality Strategies

DNA Damage Repair – BRCA & PARP

Why don't all patients respond?

Why effect to select

Critical to understand biology

- (Epi) genetic background (eg, total vs partial loss of function)
- Phenotype (not always lethal but eg, sensitizing)
- Alternative options for cells

Normal Cell

Wild type

BRCA2

2002

Cell death

Tumour Cell

Wild type BRCA2

DNA-binding Domain



2500

3418

BRCA2 del Protein

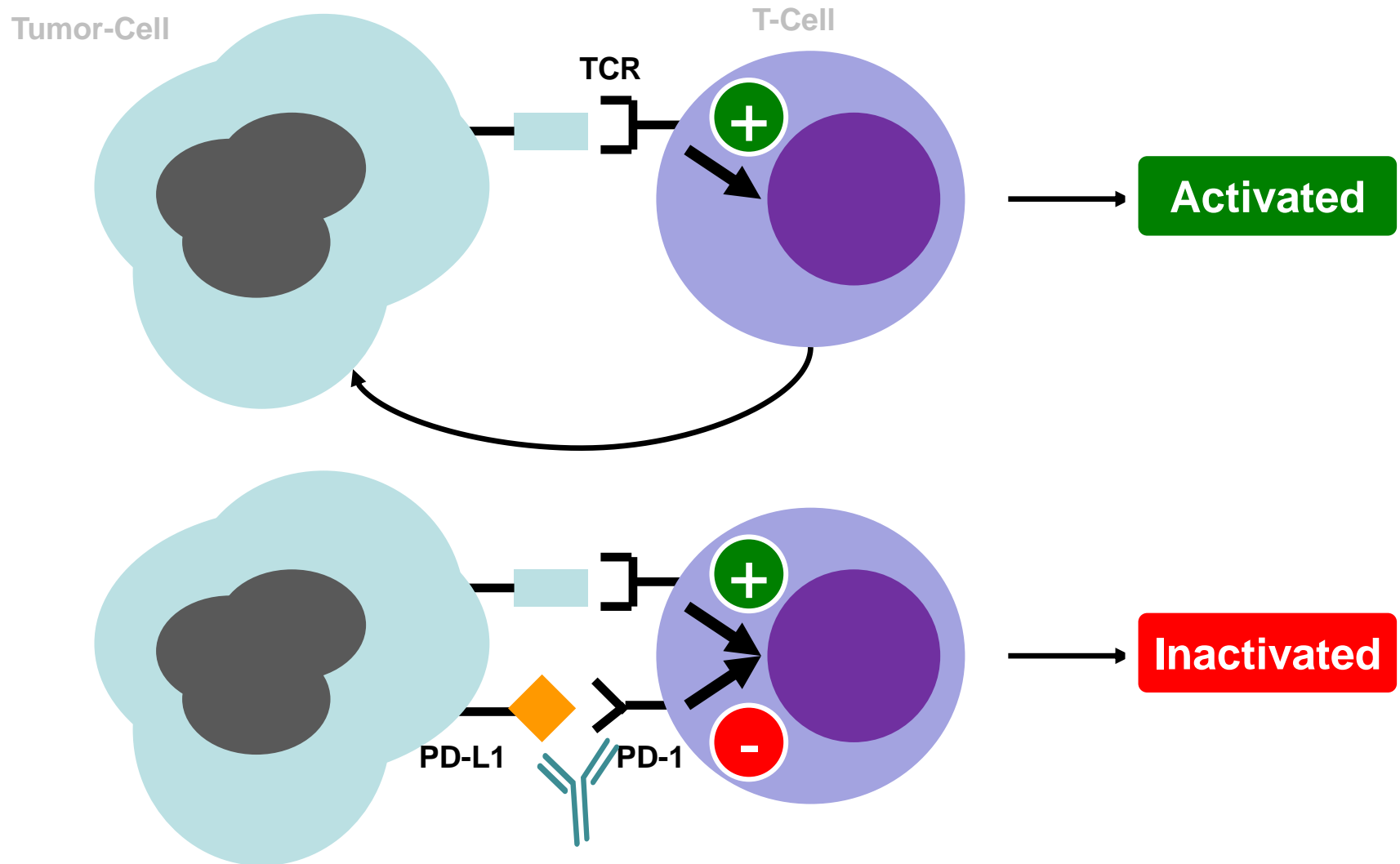


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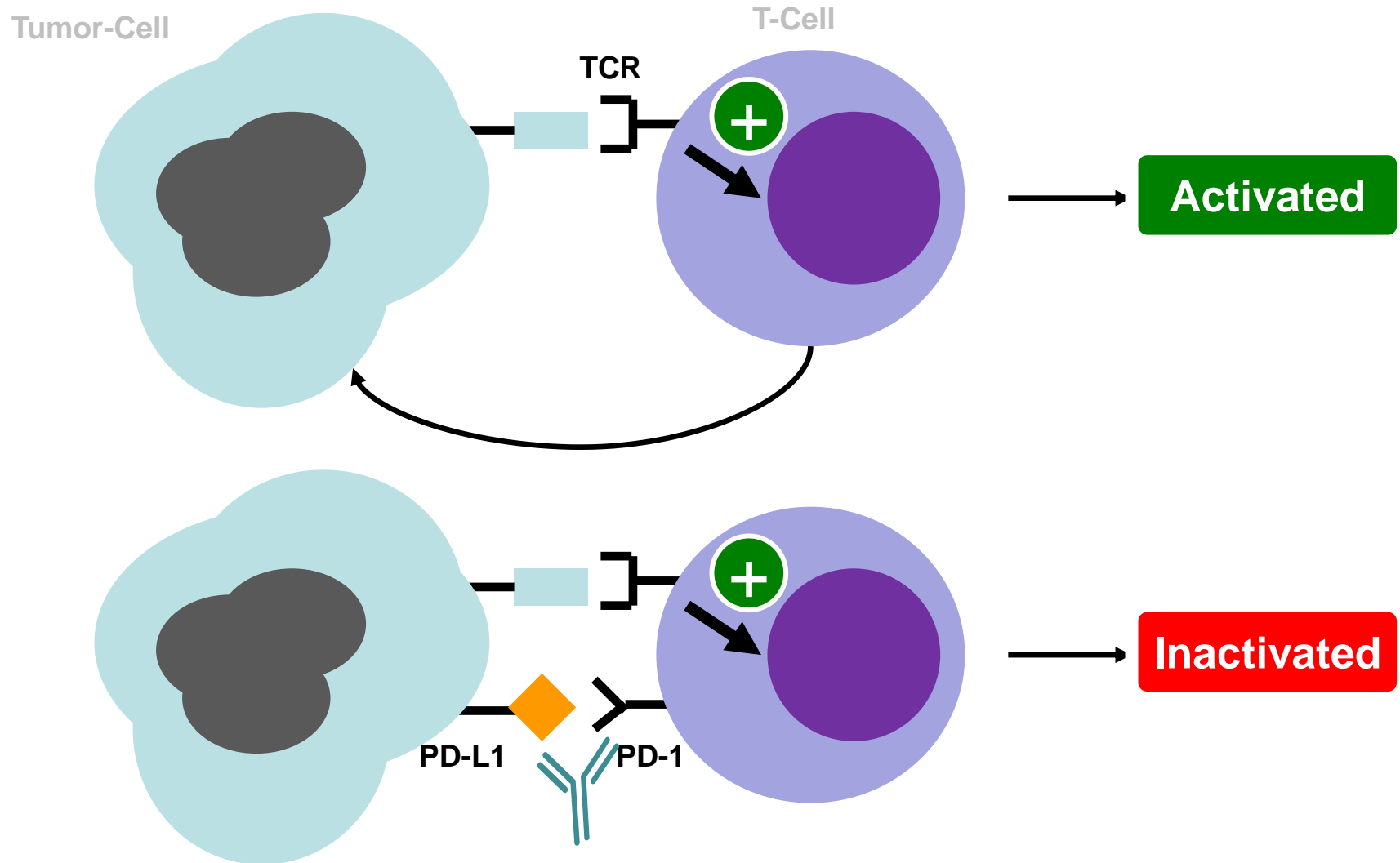
New Targets for TNBC

Targeting Immune-Checkpoints (PD-L1)



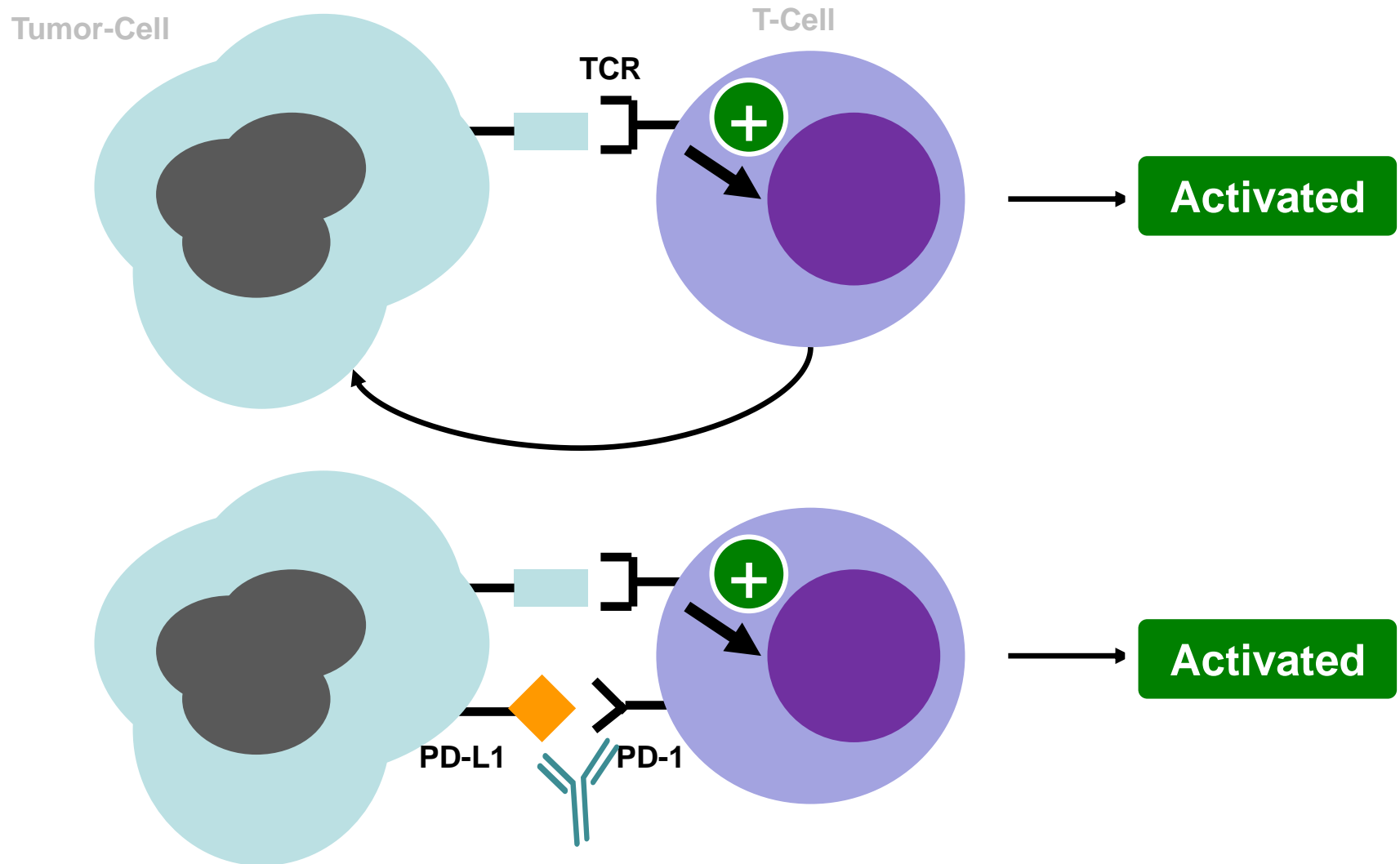
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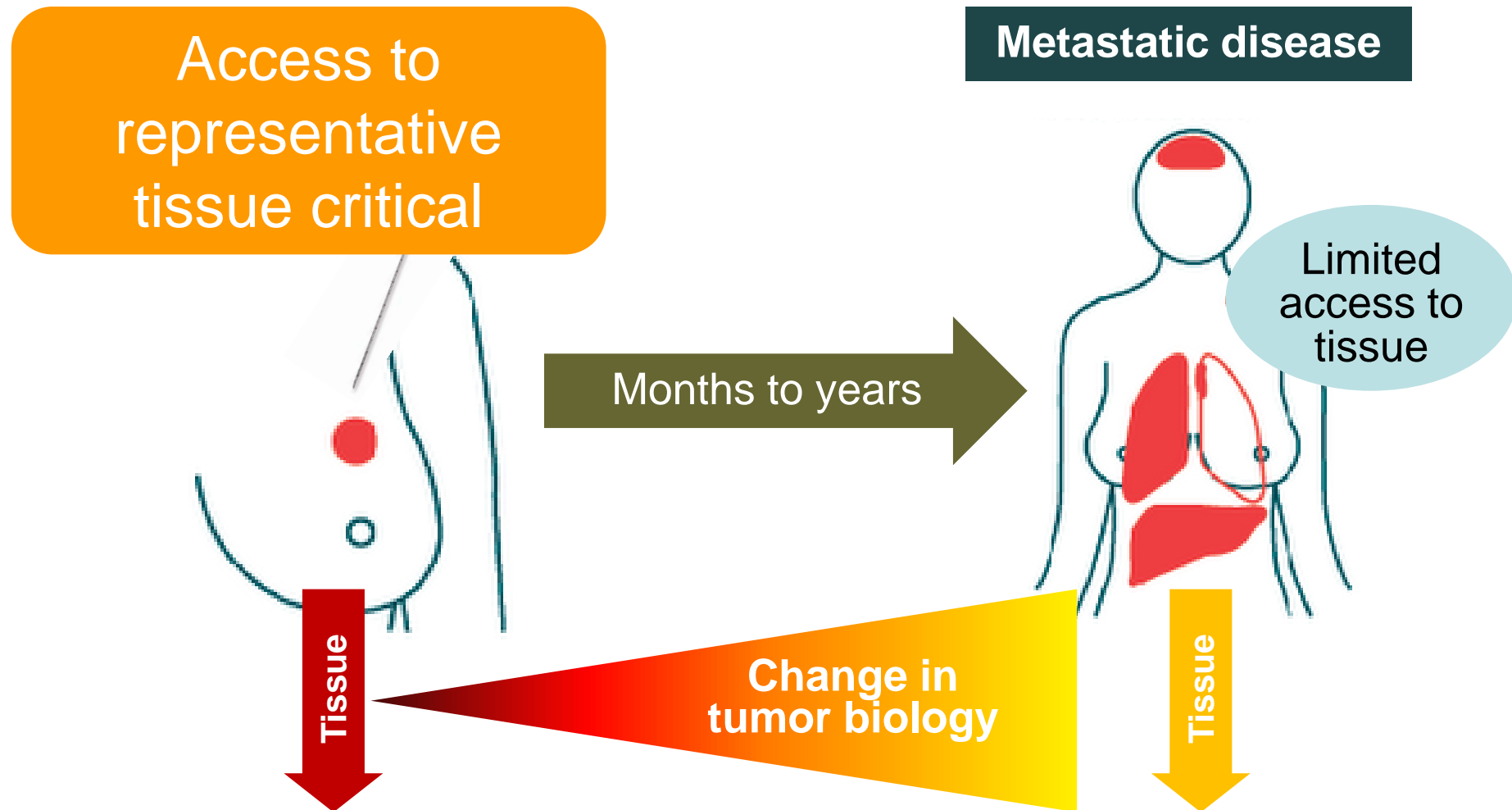
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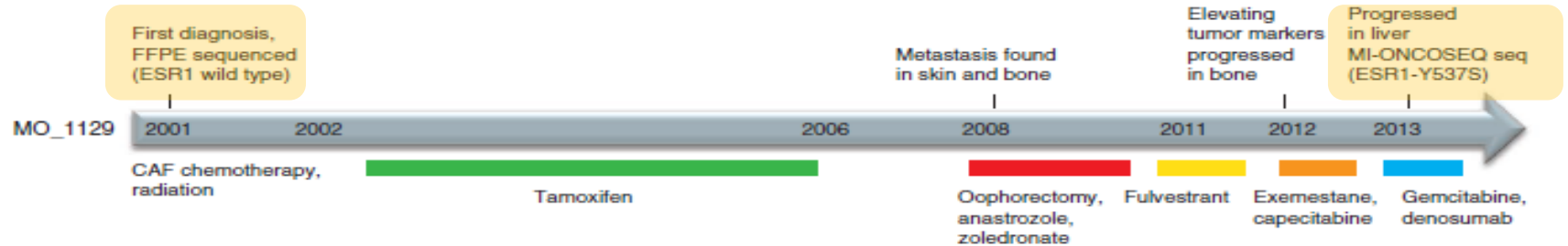
Novel Targeted Therapies and Patient Selection

Change of Tumor Biology Over Time



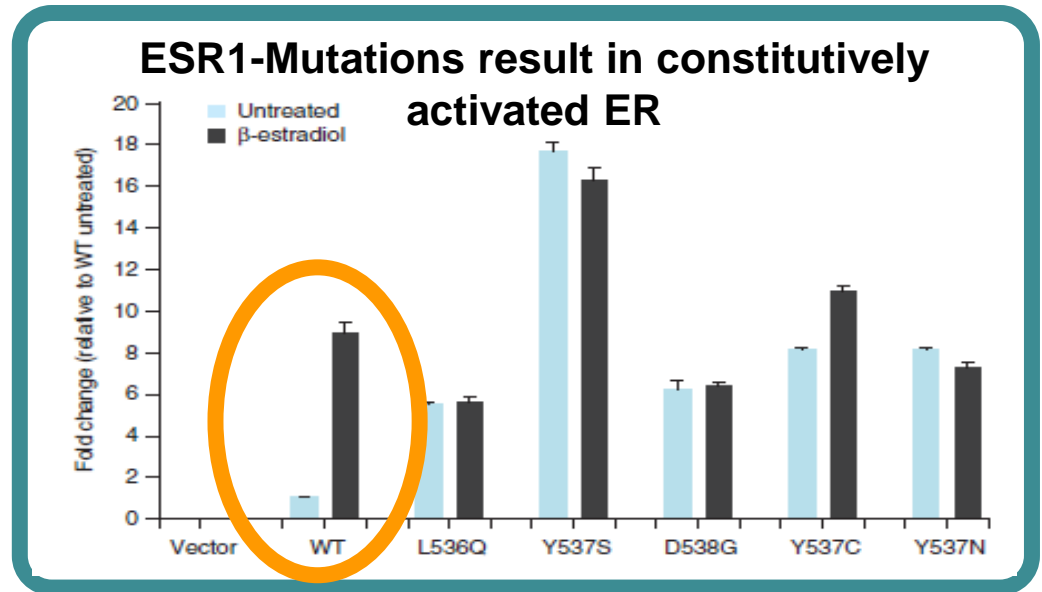
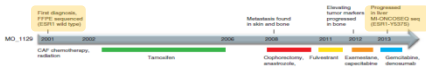
Change of Tumor Biology Over Time

Acquired ESR1 Mutations



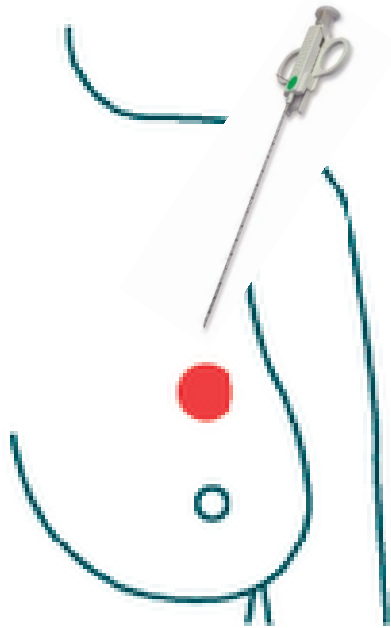
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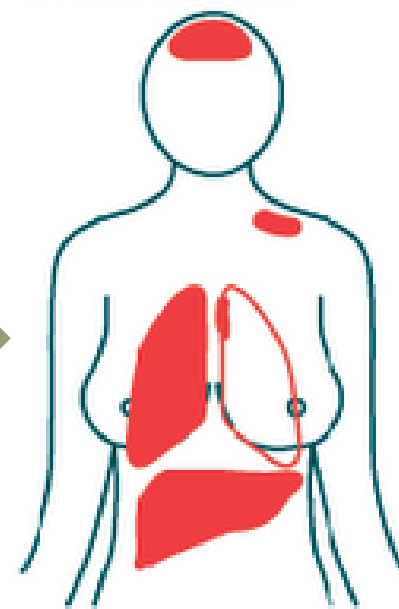


Circulating Biomarkers to Assess Dynamic Changes Genetic Profiles From cfDNA

Early breast cancer

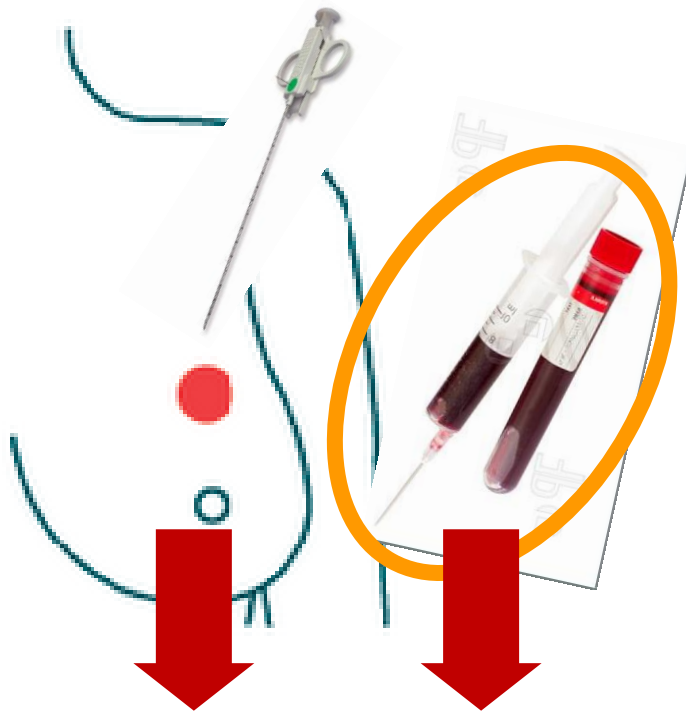


Metastatic disease



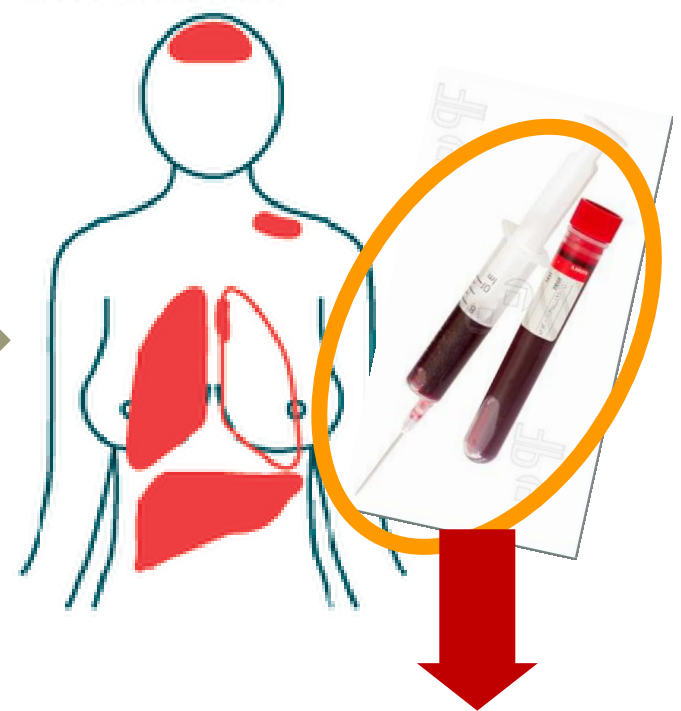
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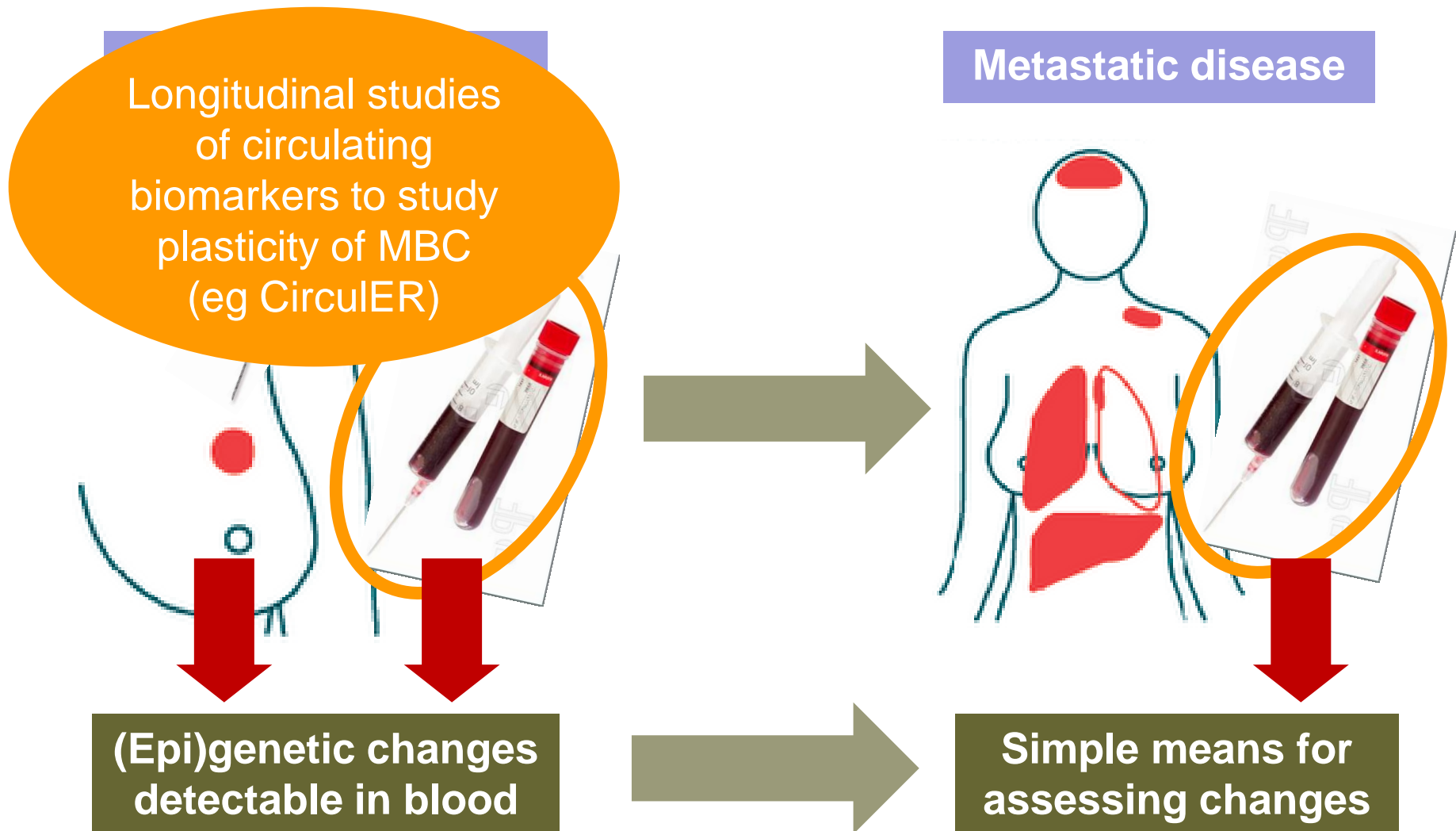
(Epi)genetic changes
detectable in blood

Metastatic disease



Simple means for
assessing changes

Circulating Biomarkers to Assess Dynamic Changes Genetic Profiles From cfDNA



Molecular Targeted Approaches to Therapy in MBC

Summary and Conclusions

- ER and HER2 remain the dominant pathways in MBC
- Crosstalk between ER or HER2 and signaling pathways is a key driver of endocrine resistance
- Combination treatment strategies (eg, with PI3K/mTOR pathway inhibitors or CDK4/6 inhibitors) can overcome resistance
- Increasing understanding of the heterogeneity of TNBC reveals new therapeutic targets (eg, DNA Damage repair, Immune checkpoints)
- Lack of biomarkers for patient selection remains challenging

Striking Success:

The Emergence of New
Targeted Treatment Strategies
for Advanced Breast Cancer

