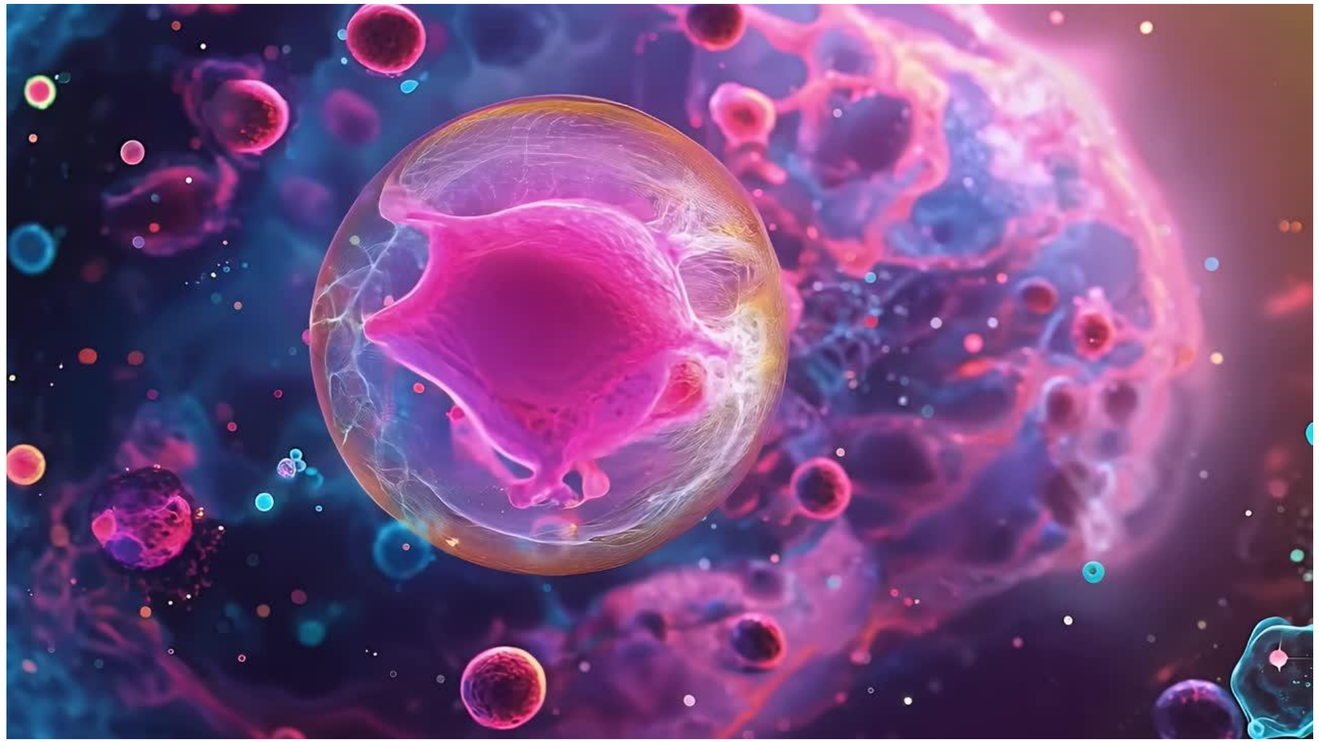
From Embryo to Tumor: Exploring Developmental Oncology



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The Wendel lab, Cancer Biology and Genetics
Memorial Sloan Kettering Cancer Center

2010-2013: B.Sc. [H] Biochemistry, University of Delhi, India

2013- 2015: M.Biotech, All India Institute of Medical Sciences, Delhi, India

2016-2021: Ph.D. Biochemistry, Weizmann Institute of Science

- Dr. Rivka Dikstein's lab
- Targeting Translation Control as a strategy for research and therapeutics

Since 2022: Postdoctoral Researcher, MSKCC

- Dr. Wendel's lab
- Developing innovative methods to create therapeutic strategies that specifically target MYC translation.

Urmila Sehrawat, Ph.D.

Today’s session:

- Connection between embryogenesis and tumorigenesis
- Reactivated developmental pathways in oncogenesis.
- The context-dependent roles of specific developmental signaling pathways.
- The therapeutic potential and limitations of targeting developmental pathways.
- In class discussions, a real-world clinical case studies.

Session Info:

- ❑ Interactive presentation (~20 mins)

Brief break 5-7 mins

Team formation: We make five teams, to continue with the rest of the session

- ❑ Kahoot Quiz on Developmental Oncology (~20 mins): Easy and Fun ☺

Brief break 5-7 mins

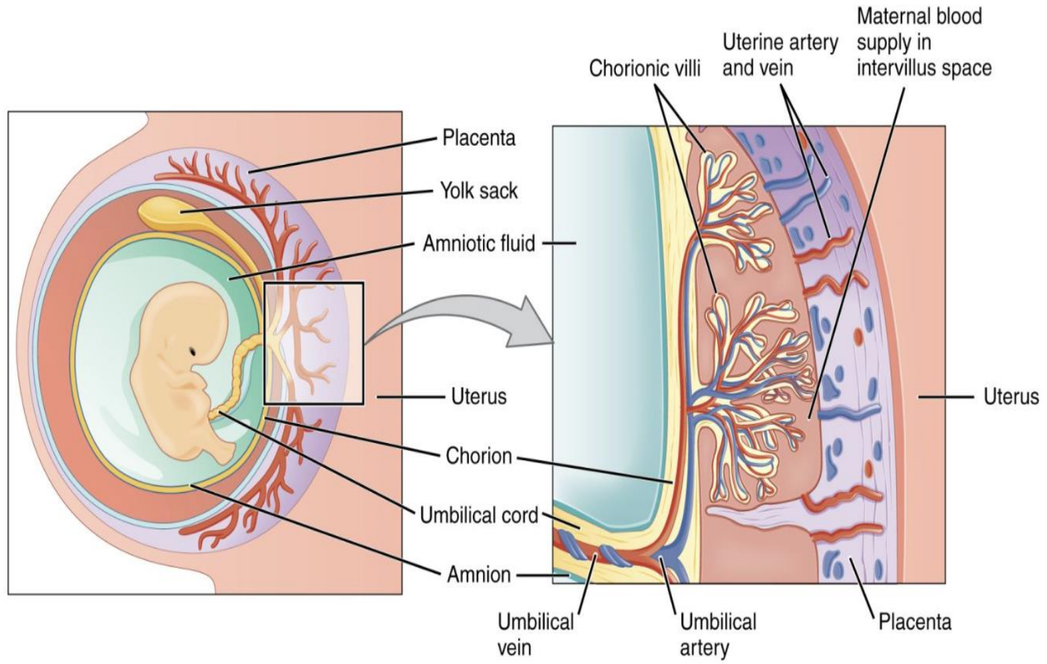
- ❑ Real-life case studies- Discussing why studying and targeting signaling pathways is critical and how we can do that as young scientists (~20 mins)

Brief break 15 mins

- ❑ In class discussion/debate on two of the provided motions. The team selects a motion and presents it for or against.

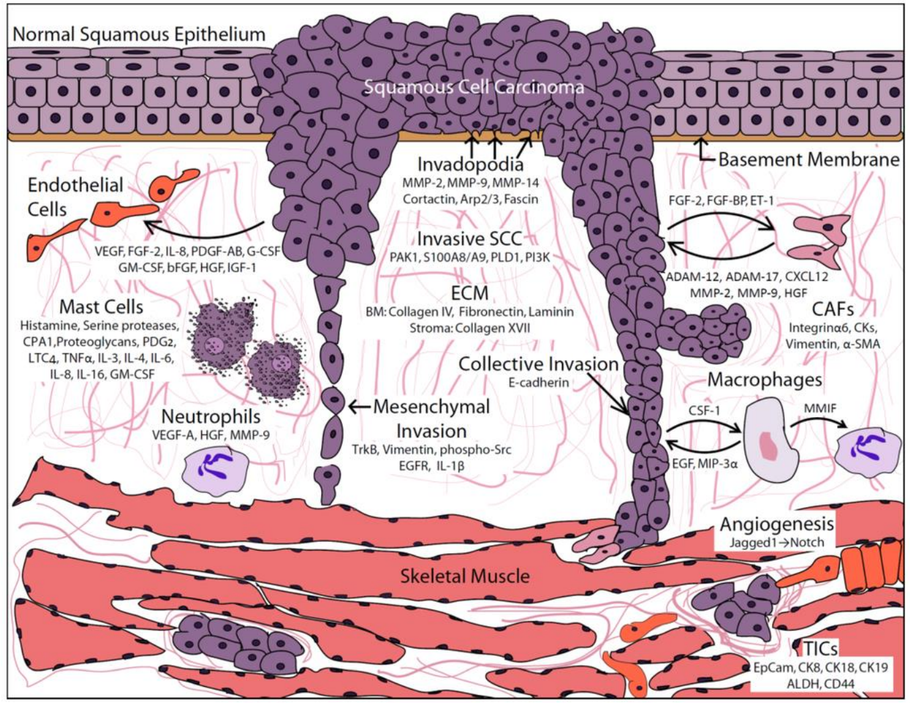
What comes to your mind when you think of

The Fetus



- Rapidly Grows
- Invades
- Manipulates the mother's immunity
- Reshapes blood vessels

The Cancer



- Rapidly Grows
- Invades
- Manipulates Immune system
- Reshapes blood vessels

What do you think the genetic composition of a Placenta would look like?

A. Normal tissue
B. Cancer cell
C. Fetus
D. Unique

Parallels between placenta and pediatric malignancies

Article

Inherent mosaicism and extensive mutation of human placentas

https://doi.org/10.1038/s41586-021-03345-1

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Check for updates

Tim H. H. Coorens[1,10], Thomas R. W. Oliver[1,2,10], Rashesh Sanghvi[1], Ulla Sovio[3], Emma Cook[3], Roser Vento-Tormo[1], Muzlifah Haniffa[1,4,5], Matthew D. Young[1], Raheleh Rahbari[1], Neil Sebire[6,7], Peter J. Campbell[1], D. Stephen Charnock-Jones[3,8,11]✉, Gordon C. S. Smith[2,3,8,11]✉ & Sam Behjati[1,2,9,11]✉

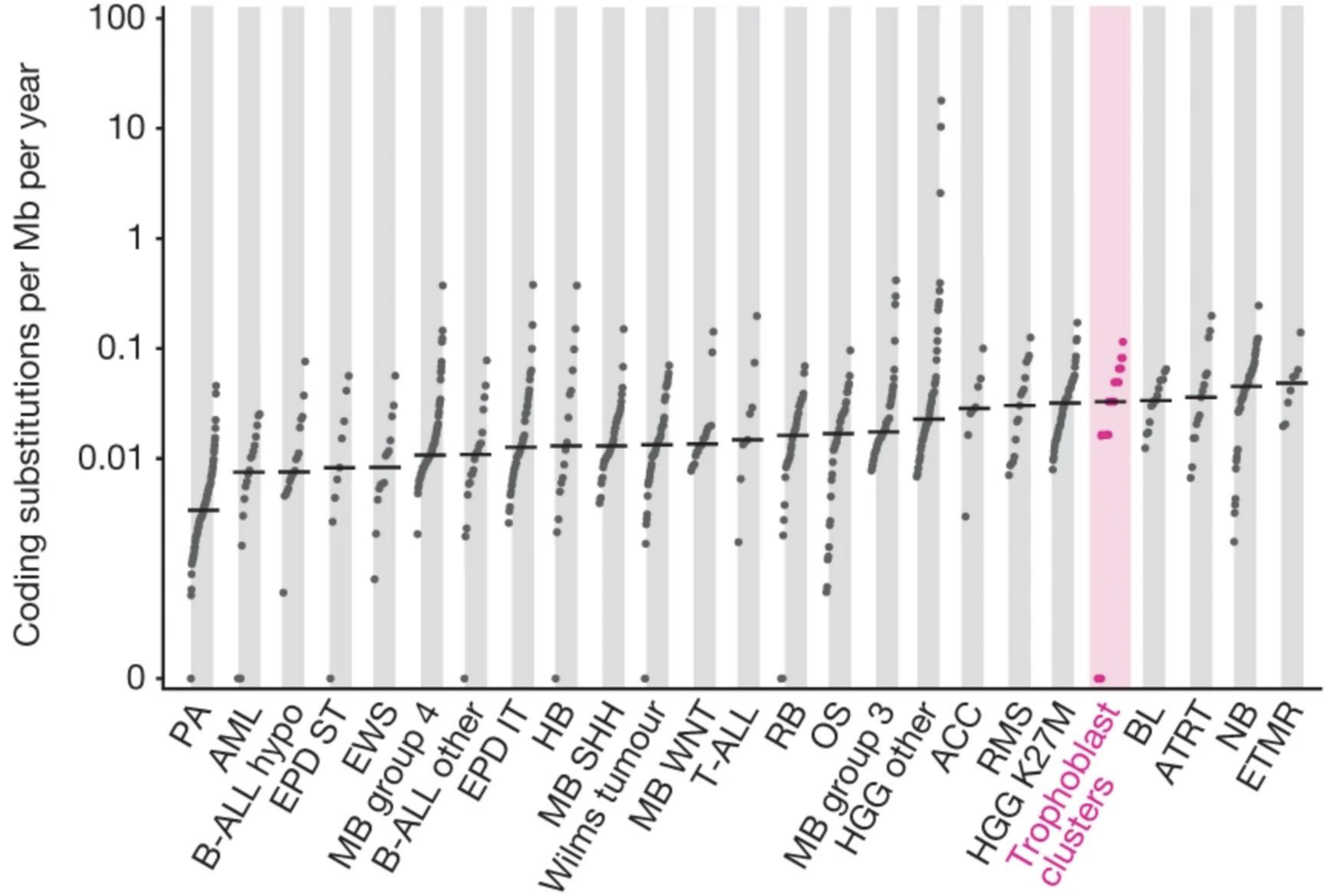
Placentas can exhibit chromosomal aberrations that are absent from the fetus[1]. The basis of this genetic segregation, which is known as confined placental mosaicism, remains unknown. Here we investigated the phylogeny of human placental cells as reconstructed from somatic mutations, using whole-genome sequencing of 86 bulk placental samples (with a median weight of 28 mg) and of 106 microdissections of placental tissue. We found that every bulk placental sample represents a clonal expansion that is genetically distinct, and exhibits a genomic landscape akin to that of childhood cancer in terms of mutation burden and mutational imprints. To our knowledge, unlike any other healthy human tissue studied so far, the placental genomes often contained changes in copy number. We reconstructed phylogenetic relationships between tissues from the same pregnancy, which revealed that developmental bottlenecks genetically isolate placental tissues by separating trophectodermal lineages from lineages derived from the inner cell mass. Notably, there were some cases with full segregation—within a few cell divisions of the zygote—of placental lineages and lineages derived from the inner cell mass. Such early embryonic bottlenecks may enable the normalization of zygotic aneuploidy. We observed direct evidence for this in a case of mosaic trisomic rescue. Our findings reveal extensive mutagenesis in placental tissues and suggest that mosaicism is a typical feature of placental development.

Placenta is a dumping ground for genetic defects

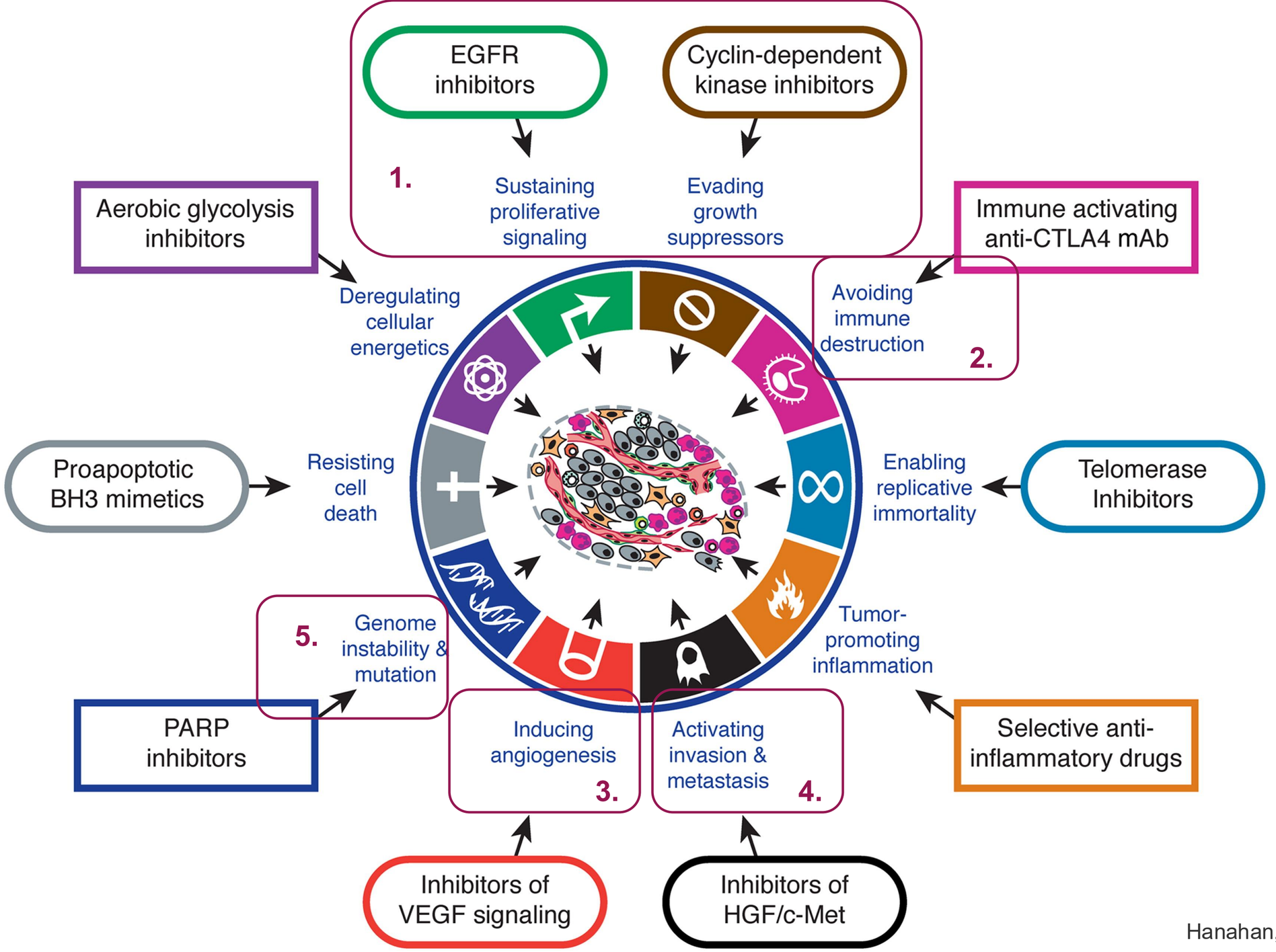
News article by the Communications Team 10 Mar 2021

The study is the first high-resolution survey of the genomic architecture of the human placenta, revealing specific patterns of mutation that are commonly found in childhood cancers

Parallels between placenta and pediatric malignancies

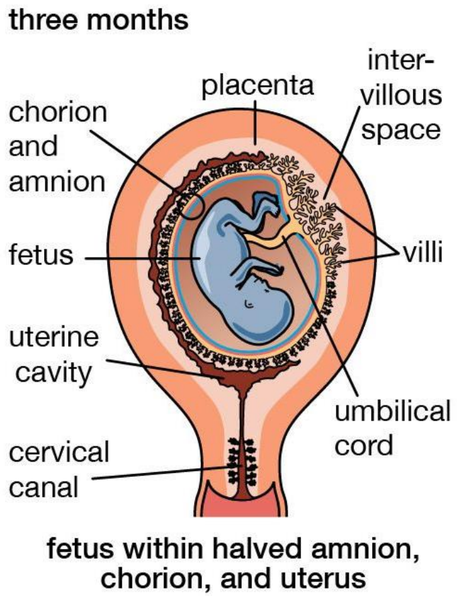


Coorens, T.H.H., Oliver, T.R.W., Sanghvi, R. *et al. 2021*



Hanahan, Douglas et al. 2011

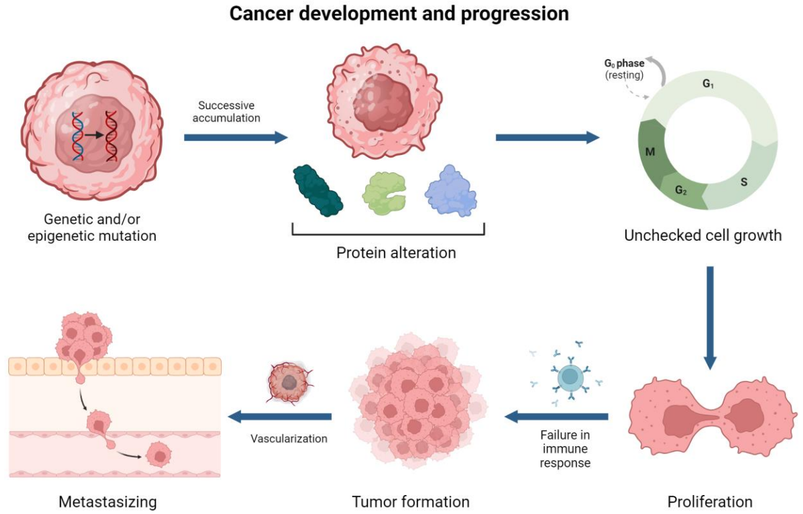
Embryo



fetus within halved amnion, chorion, and uterus

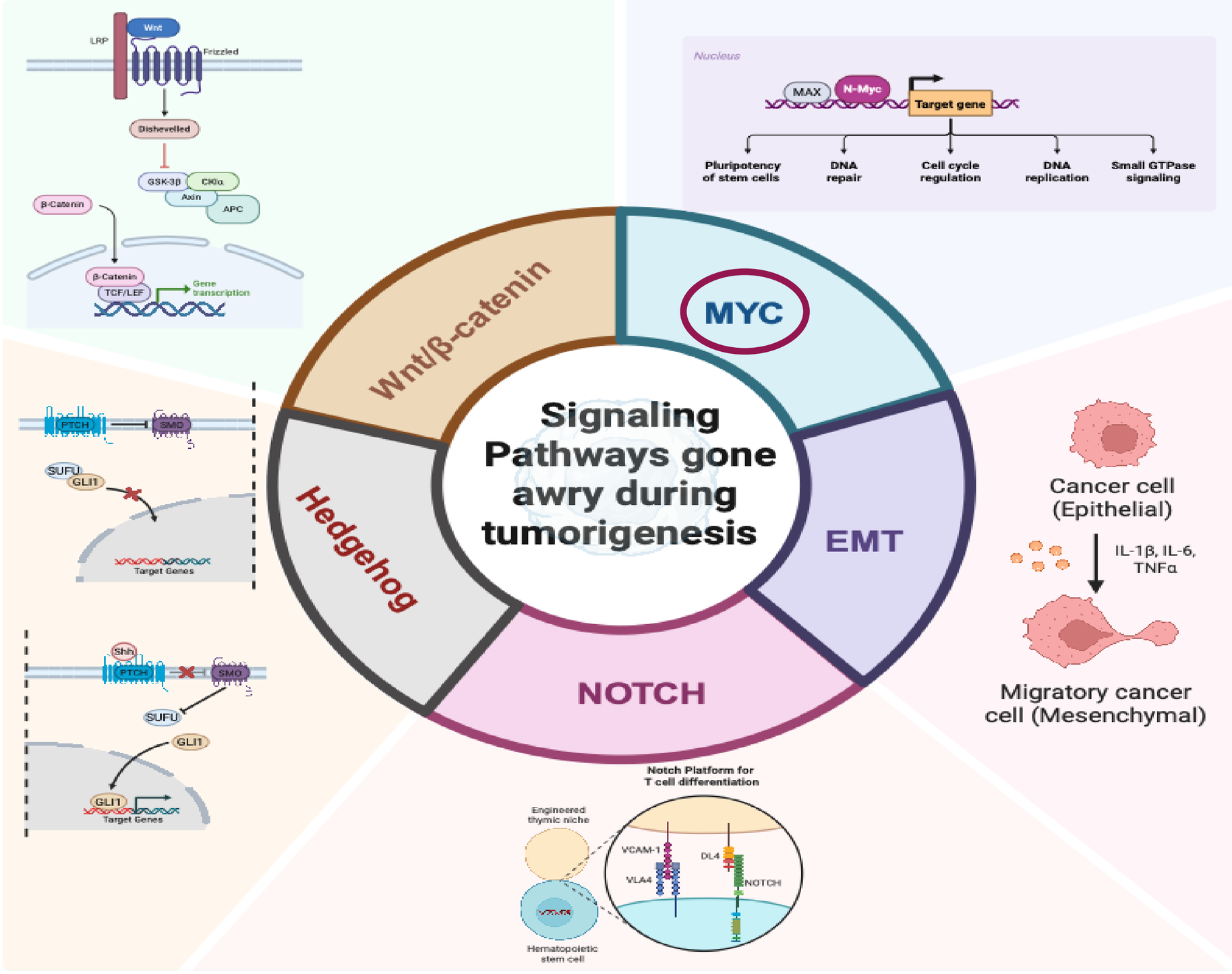
Is not

Cancer



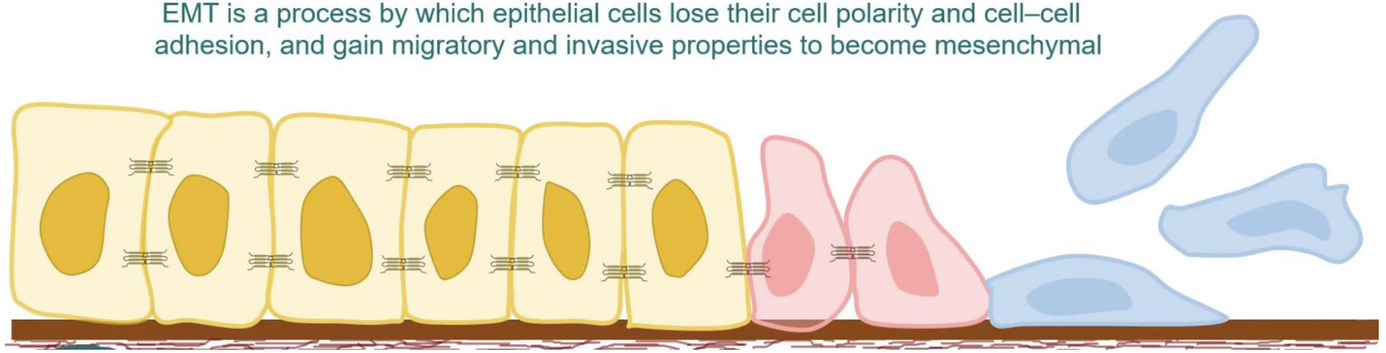
- ✓ **Tightly regulated** by gene expression to ensure proper development
- ✓ Involves **organized cell proliferation, differentiation, and migration.**
- ✓ Guided by genes **to produce a final, healthy differentiated organism**

- **Dysregulated**, with developmental pathways improperly reactivated, causing loss of control.
- Involves **uncontrolled, rapid cell proliferation**, including aberrant **migration and invasion**.
- Caused by **failures in the genetic control network**, such as mutations in tumor suppressor genes and oncogene activation

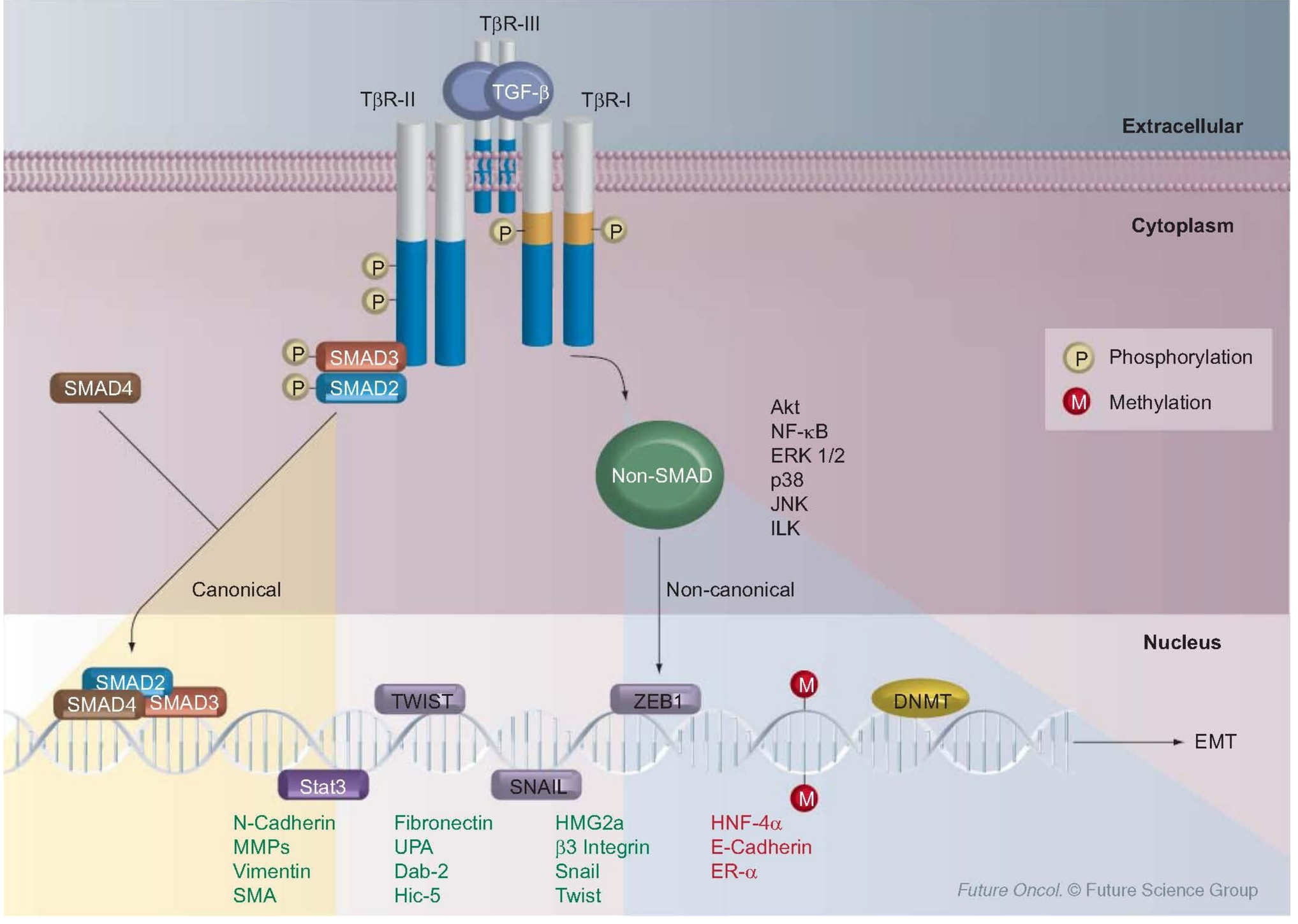

Wnt
LRP
Frizzled
Dishevelled
GSK-3β
CKIα
Axin
APC
β-Catenin
β-Catenin
TCF/LEF
Gene transcription
Nucleus
MAX
N-Myc
Target gene
Pluripotency of stem cells
DNA repair
Cell cycle regulation
DNA replication
Small GTPase signaling
Wnt/β-catenin
MYC
Signaling Pathways gone awry during tumorigenesis
Hedgehog
EMT
NOTCH
PTCH
SMO
SUFU
GLI1
Target Genes
Shh
PTCH
SMO
SUFU
GLI1
GLI1
Target Genes
Cancer cell (Epithelial)
IL-1β, IL-6, TNFα
Migratory cancer cell (Mesenchymal)
Notch Platform for T cell differentiation
Engineered thymic niche
VCAM-1
VLA4
DL4
NOTCH
Hematopoietic stem cell

Epithelial to Mesenchymal Transition

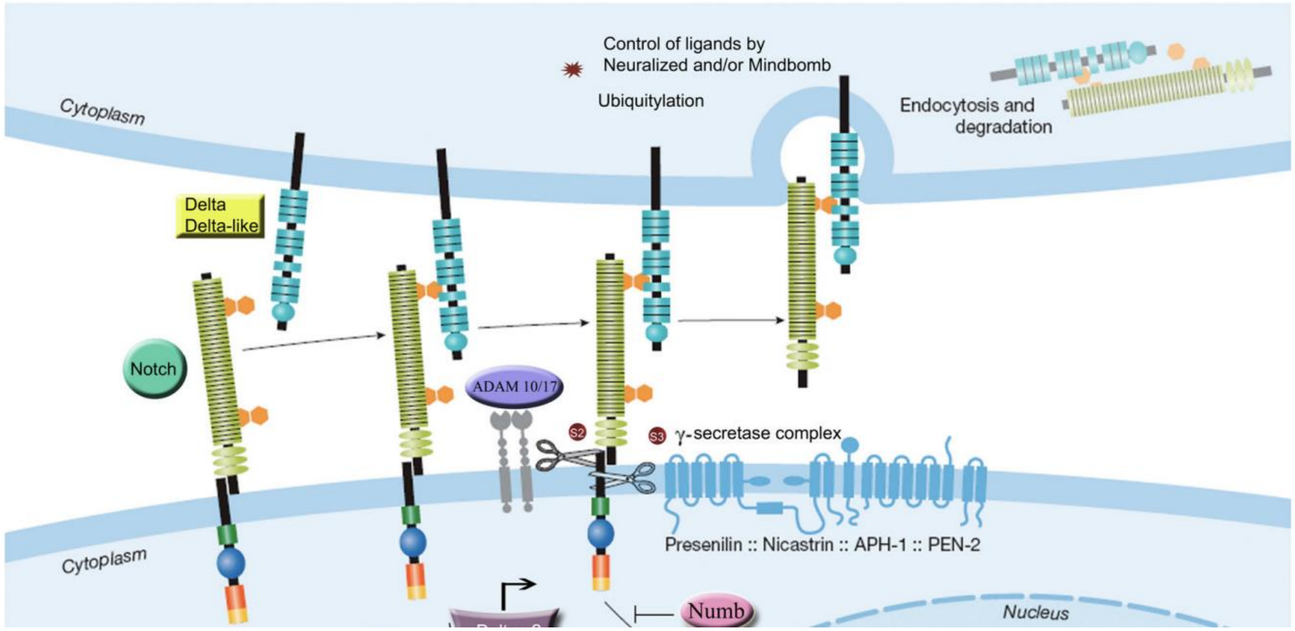
EMT is a process by which epithelial cells lose their cell polarity and cell–cell adhesion, and gain migratory and invasive properties to become mesenchymal



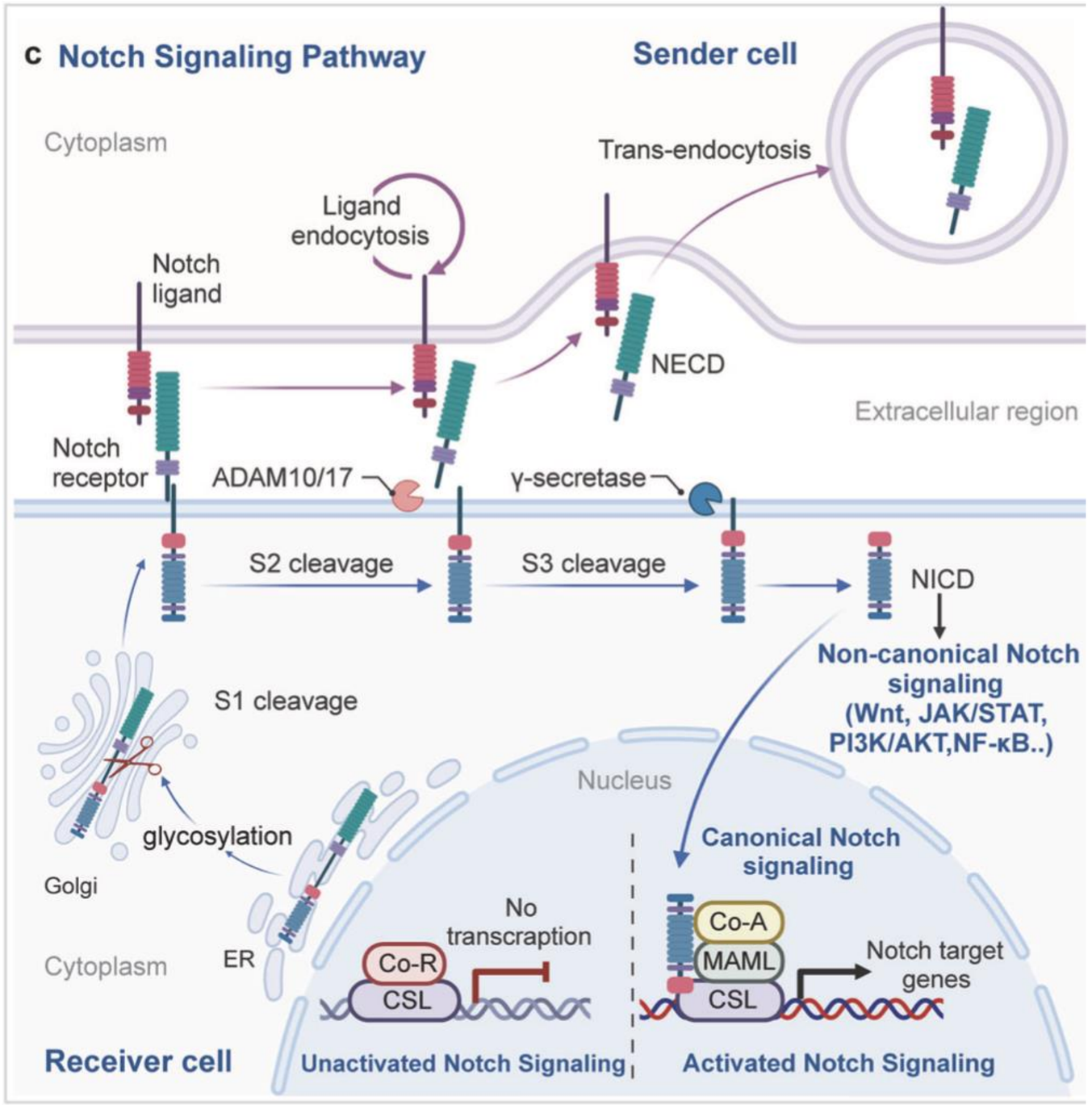
- **Epithelial-to-Mesenchymal** Transition enables **motility, invasion, and stemness**, and is essential in development and wound healing.
- Hijacked by tumors **to promote metastasis, therapy resistance, and immune evasion**.
- **No direct** EMT therapies approved.
- Emerging therapies include AXL inhibitors (bemcentinib), TGF-β inhibitors (galunisertib and bifunctional agents), and epigenetic reprogrammers (tazemetostat).
- EMT highlights how developmental plasticity enables tumor progression; targeting EMT regulators may improve therapy responses.


TβR-III
TβR-II
TGF-β
TβR-I
Extracellular
Cytoplasm
P
P
P
P
P
SMAD3
P
SMAD2
SMAD4
Non-SMAD
Akt
NF-κB
ERK 1/2
p38
JNK
ILK
P Phosphorylation
M Methylation
Canonical
Non-canonical
Nucleus
SMAD2
SMAD4
SMAD3
TWIST
ZEB1
M
DNMT
EMT
Stat3
SNAIL
M
N-Cadherin
MMPs
Vimentin
SMA
Fibronectin
UPA
Dab-2
Hic-5
HMG2a
β3 Integrin
Snail
Twist
HNF-4α
E-Cadherin
ER-α
Future Oncol. © Future Science Group

Notch Pathway

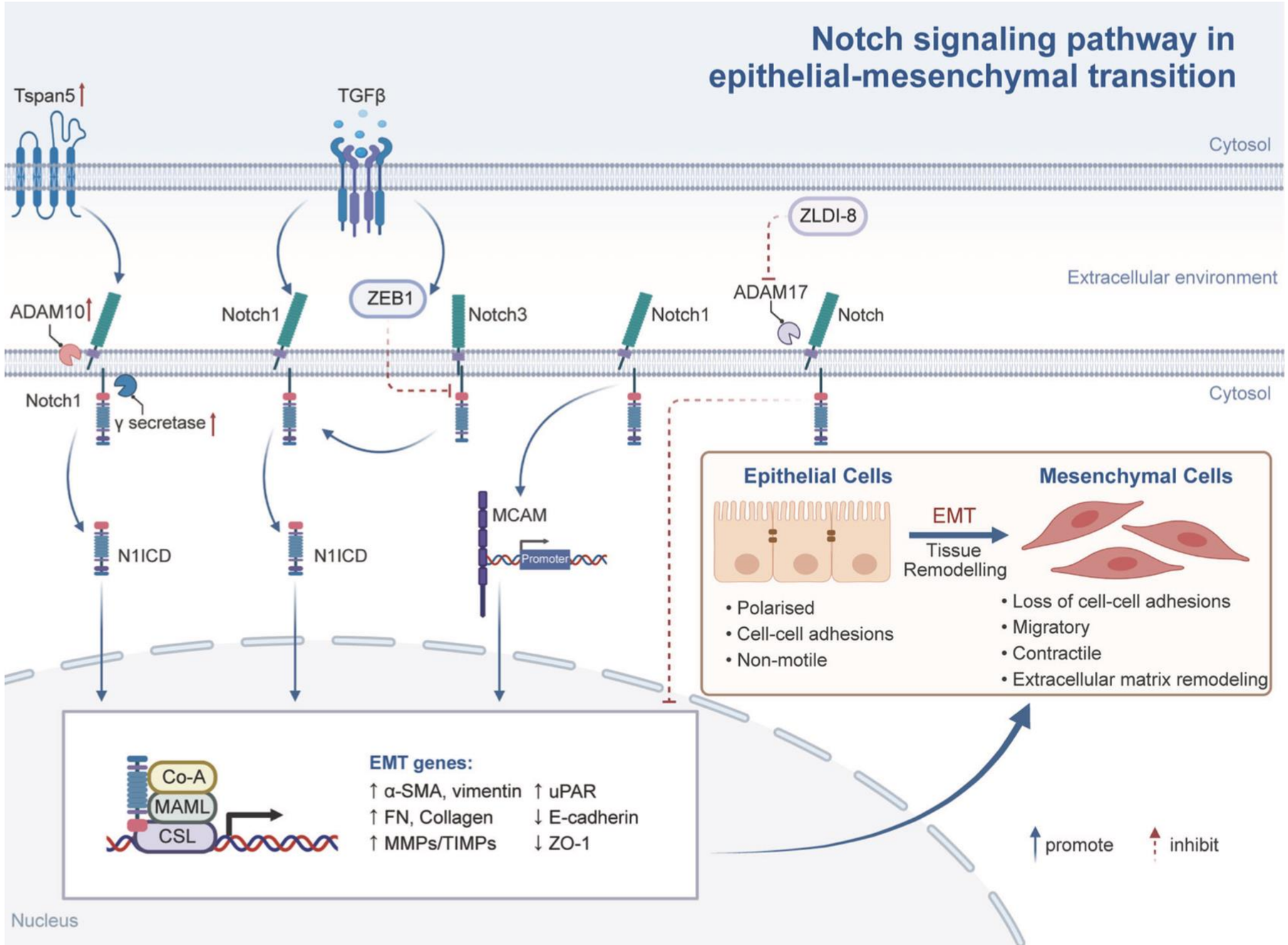


- Controls **cell fate decisions and differentiation**; highly context-dependent oncogenic vs tumor-suppressor roles
- Acts as an **oncogene in T-ALL**; a Tumor suppressor in skin and liver cancers.
- Nirogacestat (γ-secretase inhibitor) is FDA-approved for the treatment of desmoid tumors.
- **Emerging Therapies include** CB-103 (pan-Notch transcription complex inhibitor); DLL3-targeted therapies (tarlatamab in SCLC). The therapeutic window is narrow.

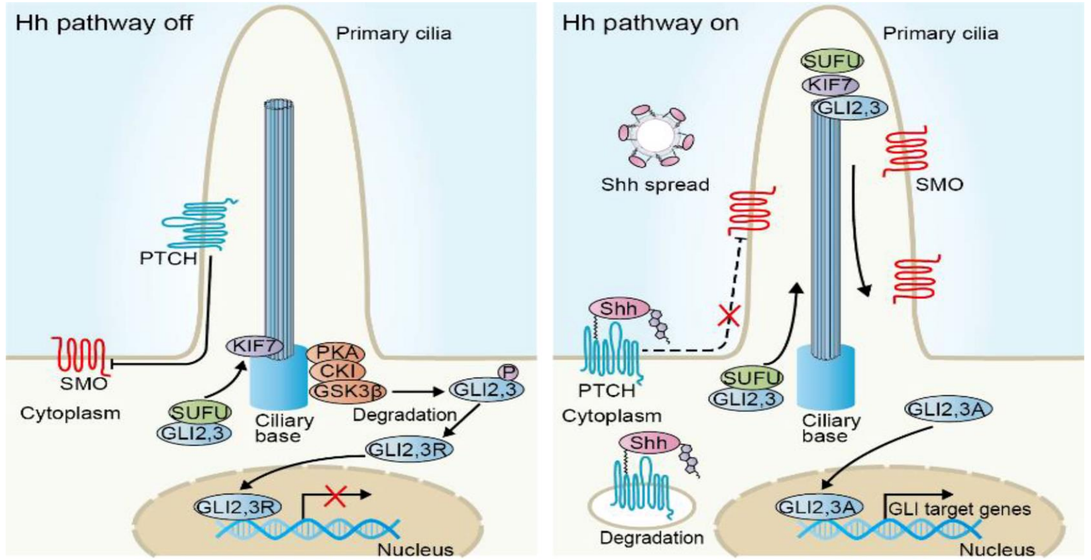


Shi et al. 2024

EMT & Notch CROSSTALK



Shi et al. 2024

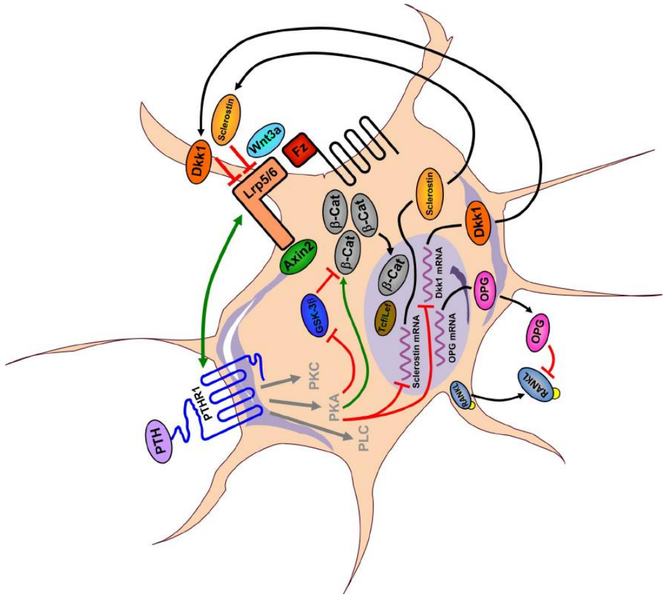


Wang J et al. 2023

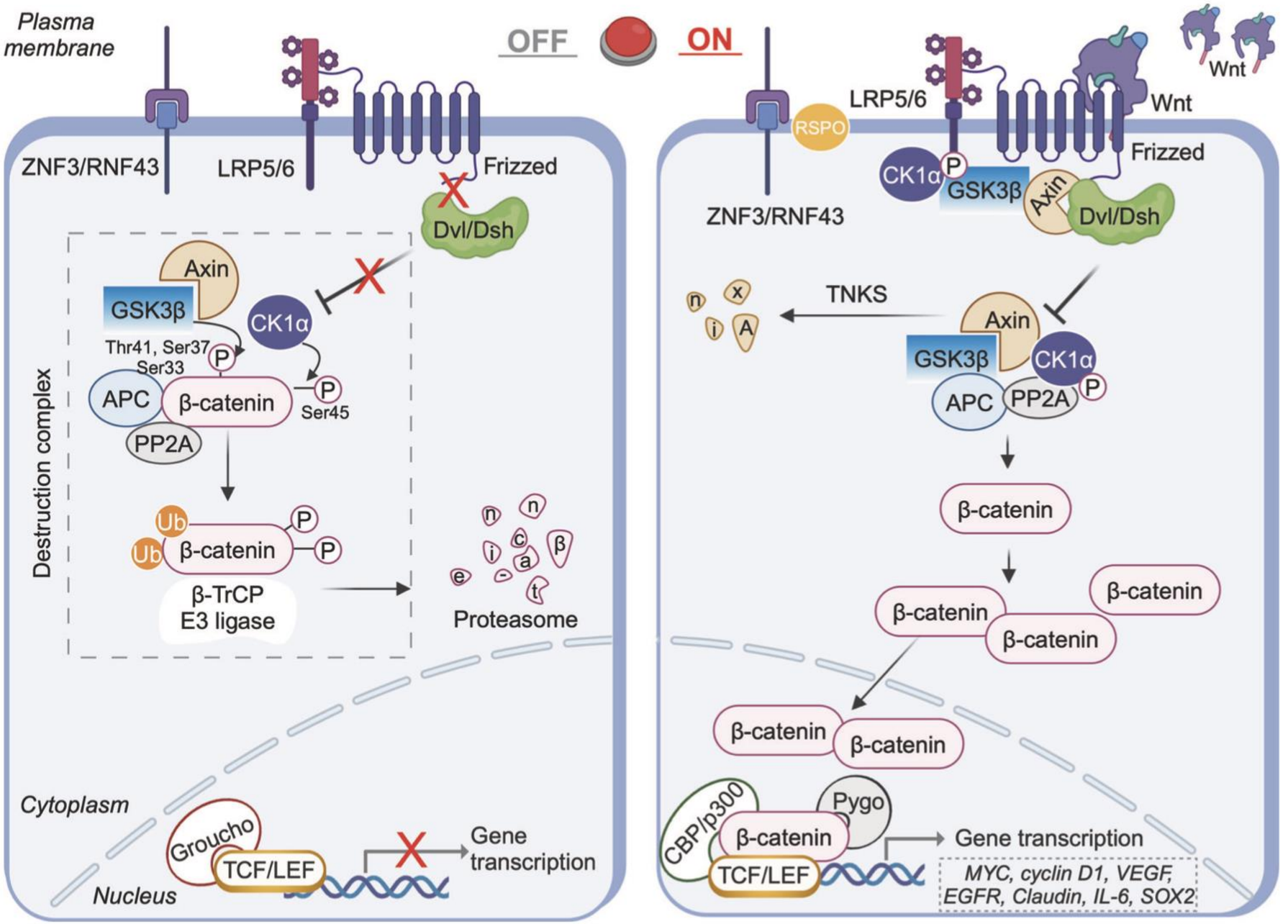
Hedgehog Pathway

- Essential in **embryonic patterning** and **organogenesis**; normally quiescent in adult tissues except in regeneration.
- Aberrant Hh activation drives **medulloblastoma, basal cell carcinoma (BCC), and subsets of AML.**
- **Approved Therapies:** Vismodegib, Sonidegib (BCC); Glasdegib (AML).
- **Novel / Emerging Therapies include GLI inhibitors in preclinical/early clinical trials and** combination approaches to overcome SMO resistance.
- **The first pathway that has multiple approved inhibitors.**

Wnt/®-catenin Pathway

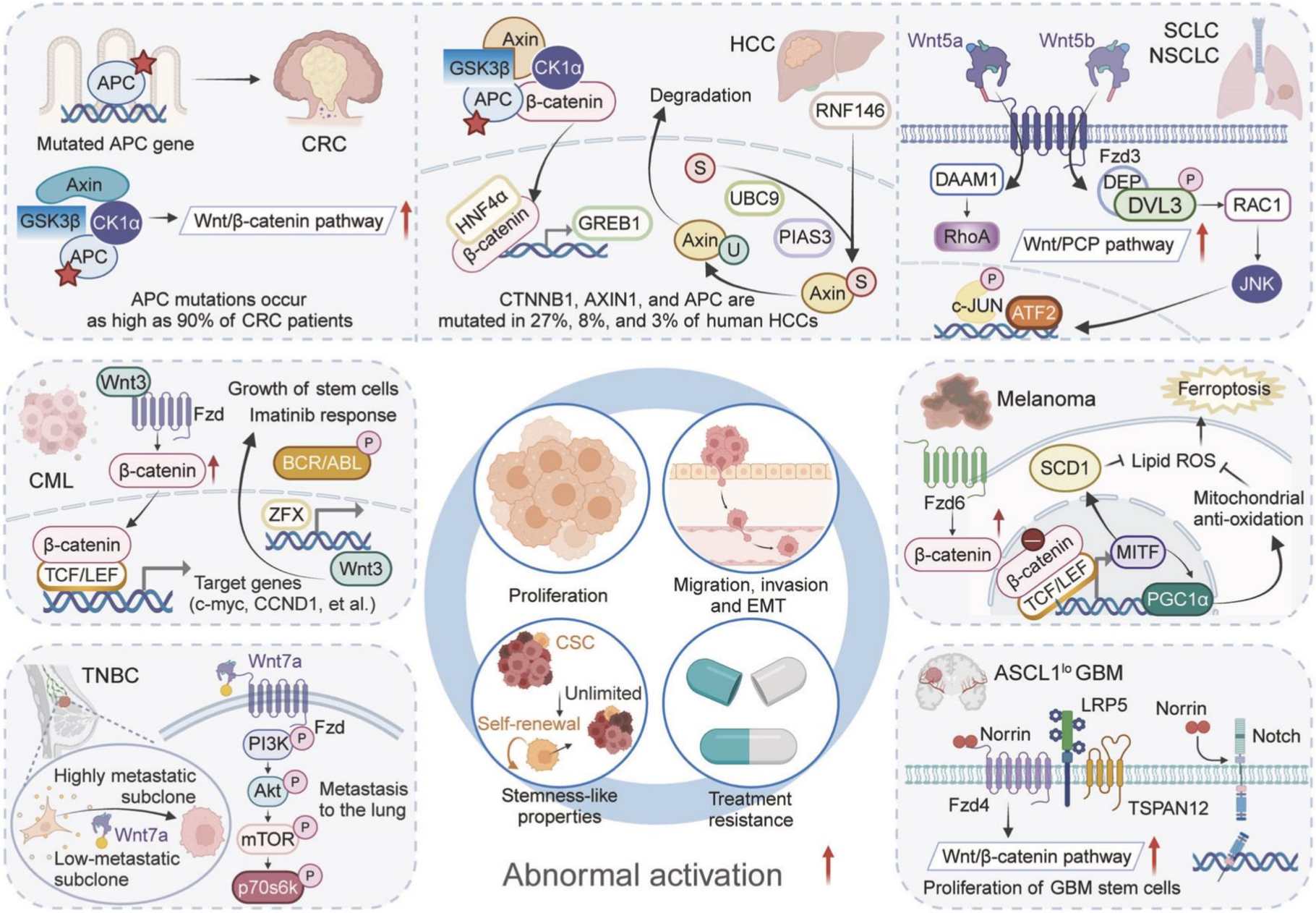


- Regulates **stem cell renewal and tissue polarity**; critical in **gut epithelium and embryogenesis**.
- Constitutive β-catenin signaling (APC loss) drives colorectal cancer; it is also implicated in liver and ovarian cancers.
- None FDA-approved;
- **Novel / Emerging Therapies:** PORCN inhibitors (RXC004, ETC-159) advancing in biomarker-driven settings; immune-oncology combos under investigation.
- Therapeutic targeting is challenging because the pathway is involved in normal stem cell niches.

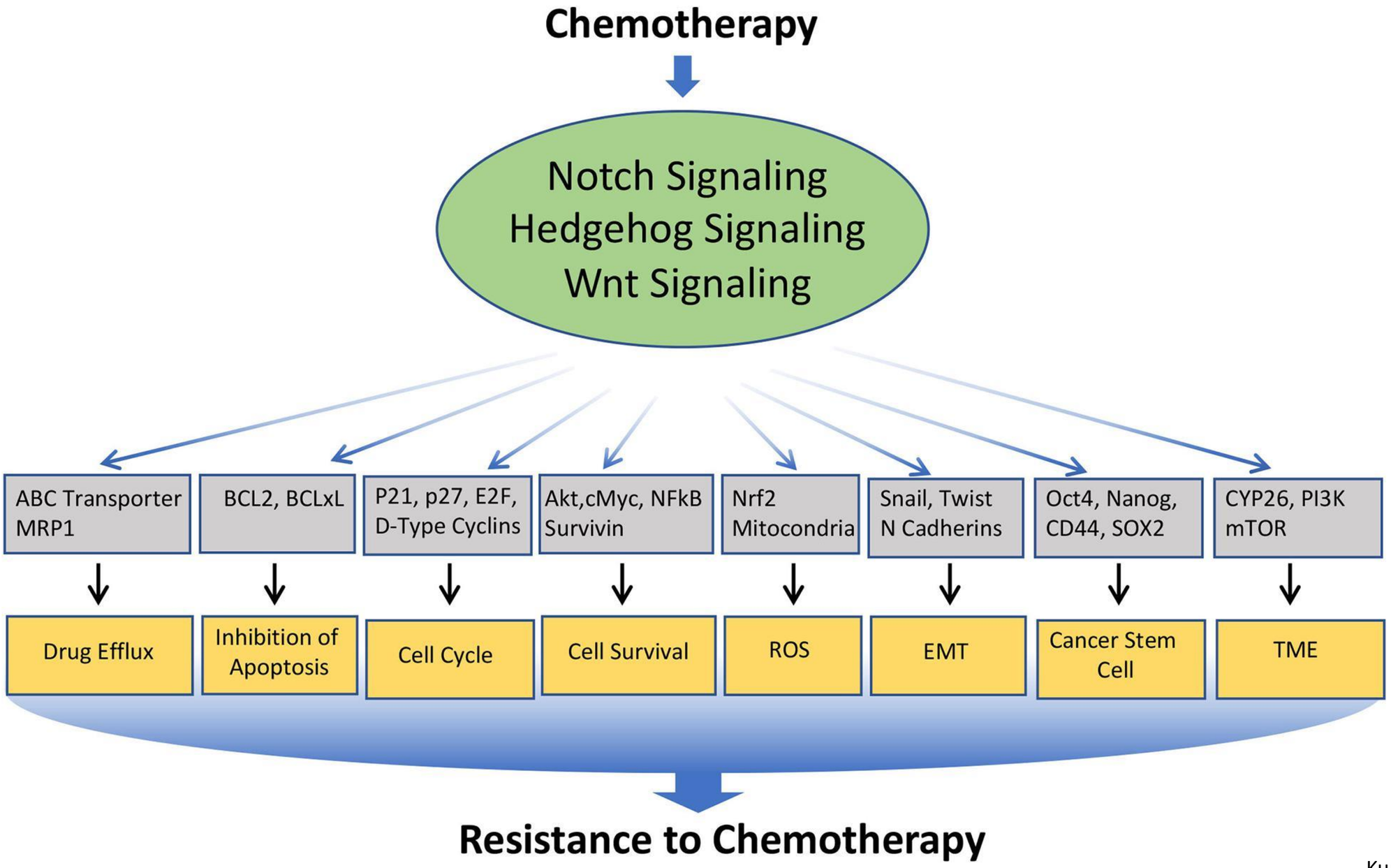


Xue C et al. 2024

Wnt signaling pathway in various cancers



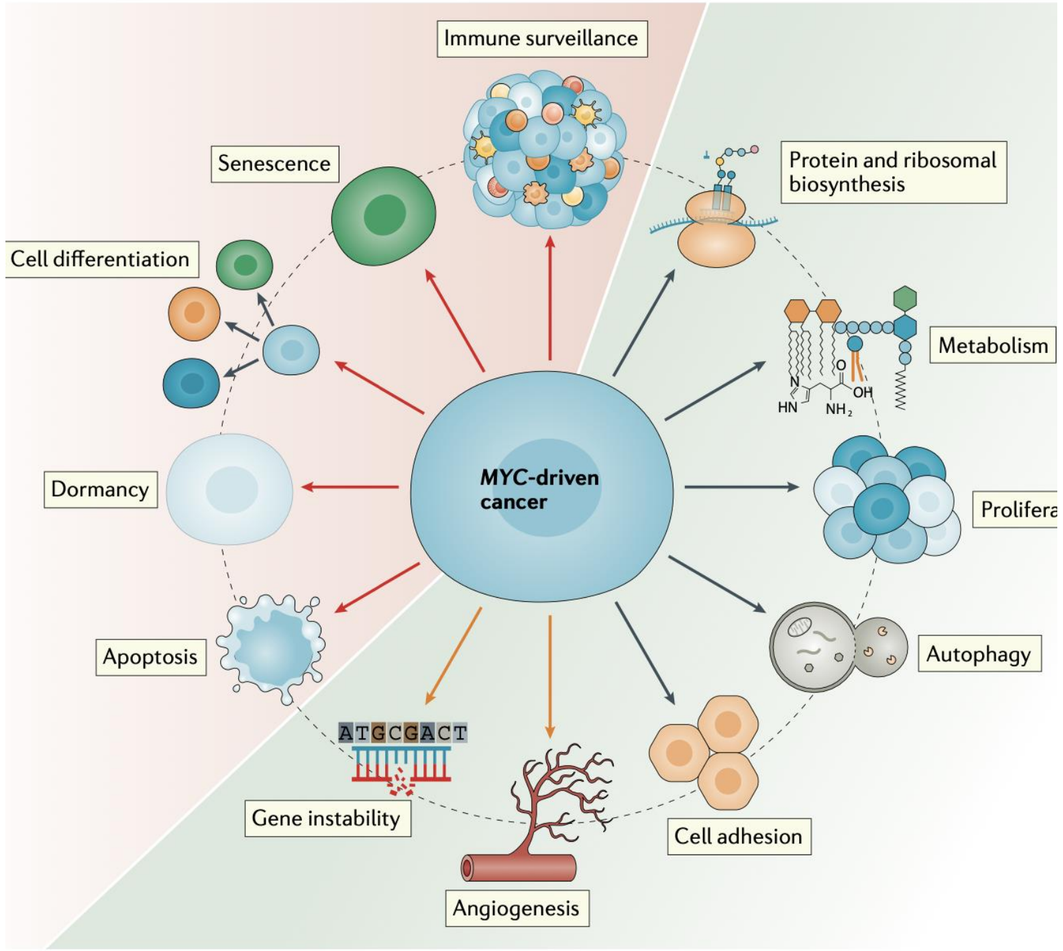
Xue C et al. 2024



Kumar V. et al. 2021

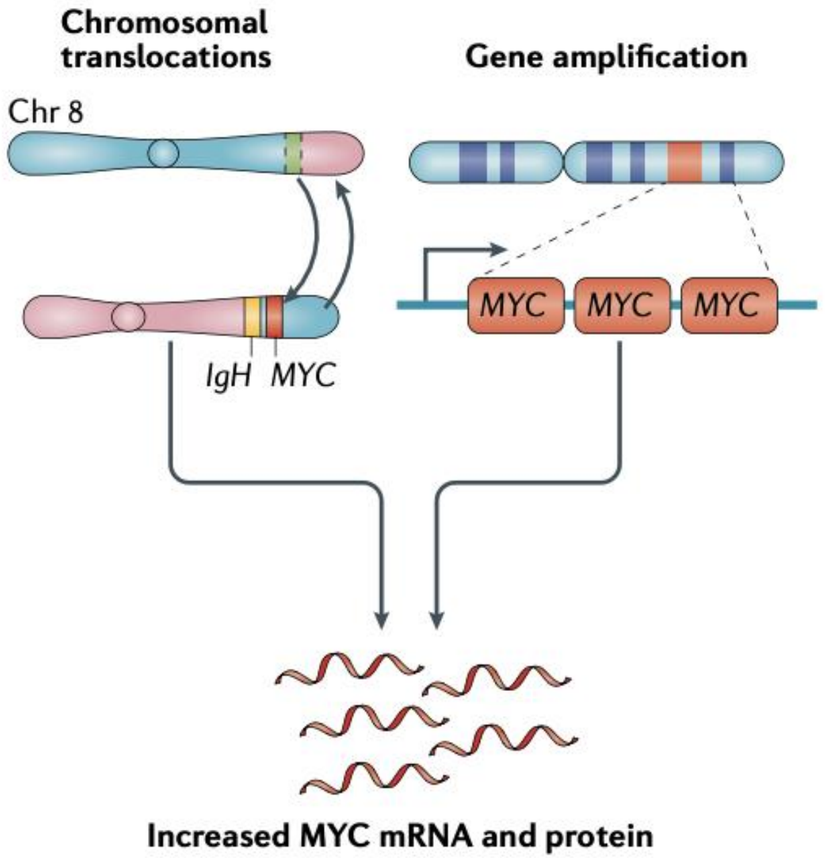
MYC

- **a key regulator that is involved in many different signaling pathways**
- Overexpression drives many cancers
- None FDA-approved; historically ‘undruggable’.
- **Novel / Emerging Therapies:** eIF4A inhibitors indirectly suppress MYC translation. OMO-103 (Omomyc mini-protein) etc.
- MYC is central to oncogenesis but difficult to drug; indirect targeting strategies are most promising.



Dhanasekaran R et al. 2022

a Genetic aberrations



Brief break ~10 mins
Stretch a little &
Make teams for the Kahoot Quiz

Case Study

Case 1: The NOTCH1 Mutation in T-Cell Acute Lymphoblastic Leukemia (T-ALL)

Clinical Summary:
A 9-year-old boy presents with fatigue, enlarged lymph nodes, and high white blood cell count. Bone marrow analysis reveals >85% immature T-cells expressing CD3 and CD7. Whole-exome sequencing identifies a NOTCH1 gain-of-function mutation, leading to constitutive activation of the Notch signaling pathway.

Mechanistic Insight:
In normal thymic development, **Notch1** signaling regulates the commitment of lymphoid progenitors toward the **T-cell lineage**, ensuring proper timing of proliferation and differentiation. The **mutation causes continuous NICD activation**, even without ligand binding, driving uncontrolled proliferation and blocking differentiation—mimicking a “locked developmental state.”

Therapeutic Context:
Treatment with **γ-secretase inhibitors (GSIs)** shows initial tumor reduction in preclinical models but is limited by gastrointestinal toxicity and relapse due to feedback reactivation of alternative pathways (e.g., PI3K/AKT).

Discussion Questions:
1.How does aberrant Notch signaling mimic developmental processes during thymocyte differentiation?
2.What are the risks of targeting a pathway essential for regular tissue maintenance?
3.Could context-dependent inhibition (ligand- or receptor-specific) improve therapeutic outcomes?

In normal thymic development

- Notch1 directs lymphoid progenitors to T-cell lineage by activating programs that promote proliferation and stop early differentiation.
- The gain-of-function mutation in NOTCH1 mimics this developmental “on” state indefinitely, keeping cells in an undifferentiated, proliferative early thymocyte-like phase.
- **Basically, the cancer cells stay caught in an endless cycle of development**.

Notch signaling is critical for homeostasis in multiple tissues

- Systemic inhibition of intestinal stem cells, hematopoietic progenitors, and vascular endothelium can lead to serious side effects.
- Gastrointestinal toxicity, Anemia, and impaired tissue regeneration.
- Unmet need for selective targeting (e.g., receptor- or ligand-specific inhibition, temporal modulation) to spare normal developmental functions.

Context-dependent inhibition (ligand- or receptor-specific) improves therapeutic outcomes.

- reduce off-target toxicity while preserving physiological Notch signaling.
- Potential Combination therapies — γ-secretase inhibitors with glucocorticoids or PI3K inhibitors
  may further improve specificity and therapeutic window by countering pathway redundancy.

Case 2: MYC Amplification in Neuroblastoma

Clinical Summary:
A 3-year-old girl presents with an abdominal mass and elevated catecholamine metabolites. Imaging confirms a large adrenal tumor with bone marrow metastases. Biopsy shows **poorly differentiated neuroblasts** with **MYCN amplification**, a hallmark of high-risk neuroblastoma.

Mechanistic Insight:
During embryonic development, **MYCN** regulates neural crest cell proliferation, migration, and differentiation. In neuroblastoma, **MYCN amplification** reactivates these proliferative programs, preventing terminal differentiation and promoting stem-like properties. The tumor exhibits high protein synthesis and metabolic reprogramming driven by the eIF4A–MYC axis.

Therapeutic Context:
Directly targeting MYC remains challenging (“undruggable”). Current strategies focus on **translation inhibitors (e.g., eIF4A blockers)** could be beneficial.

Discussion Questions:
1.How does MYCN amplification hijack developmental programs of neural crest differentiation?
2.Why is MYC considered “undruggable”?
3.What therapeutic strategies exploit MYC’s downstream vulnerabilities, and why they can or can’t work?

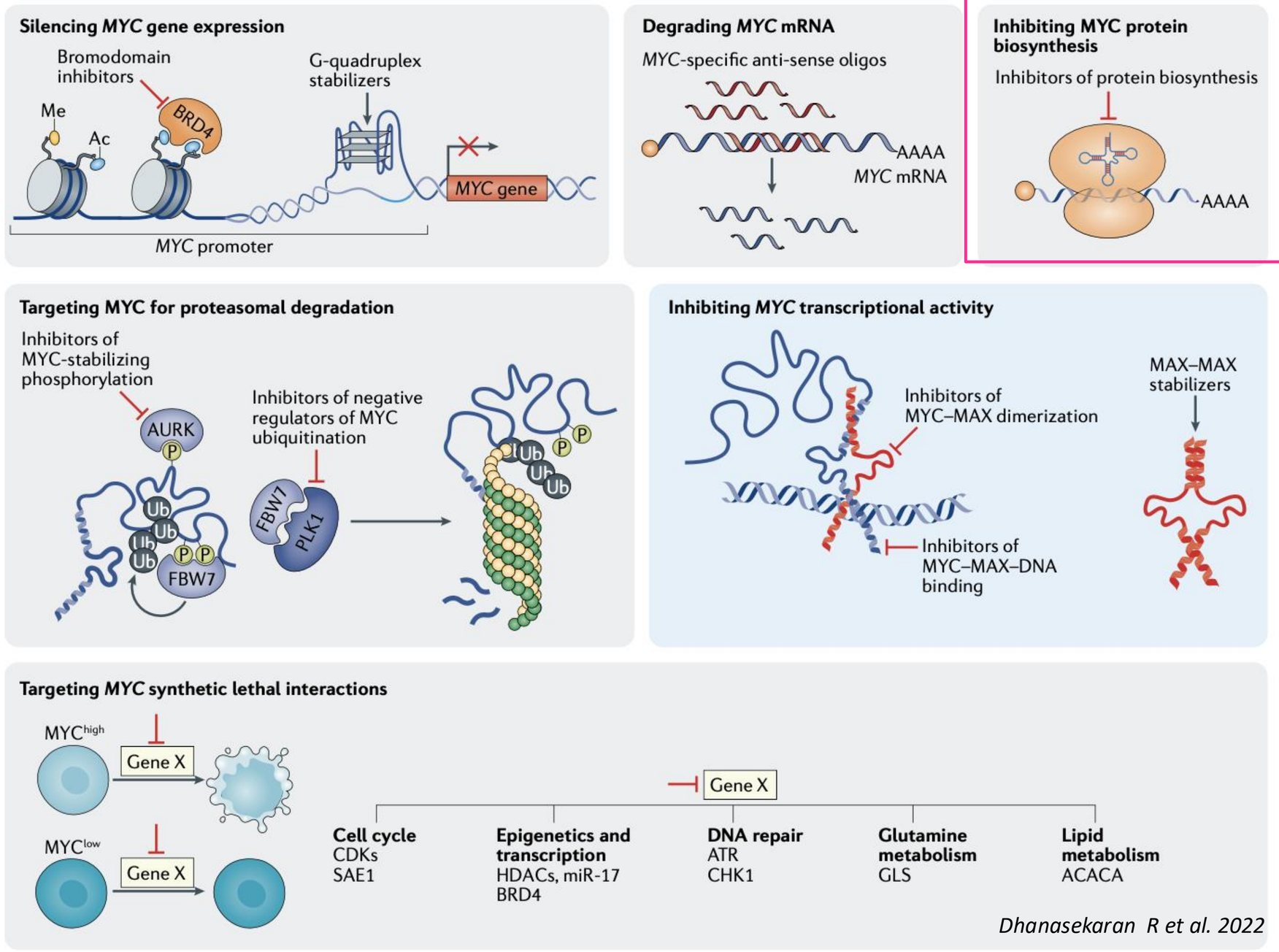
In normal development

- MYCN controls neural crest cell growth and timing of differentiation during embryogenesis.
- Amplification of MYCN reactivates embryonic proliferation, causing uncontrolled cell division and blocking differentiation.
- Tumor cells resemble “frozen” neural progenitors — proliferative but unable to mature — a hallmark of developmental reprogramming in cancer.

MYC is undruggable

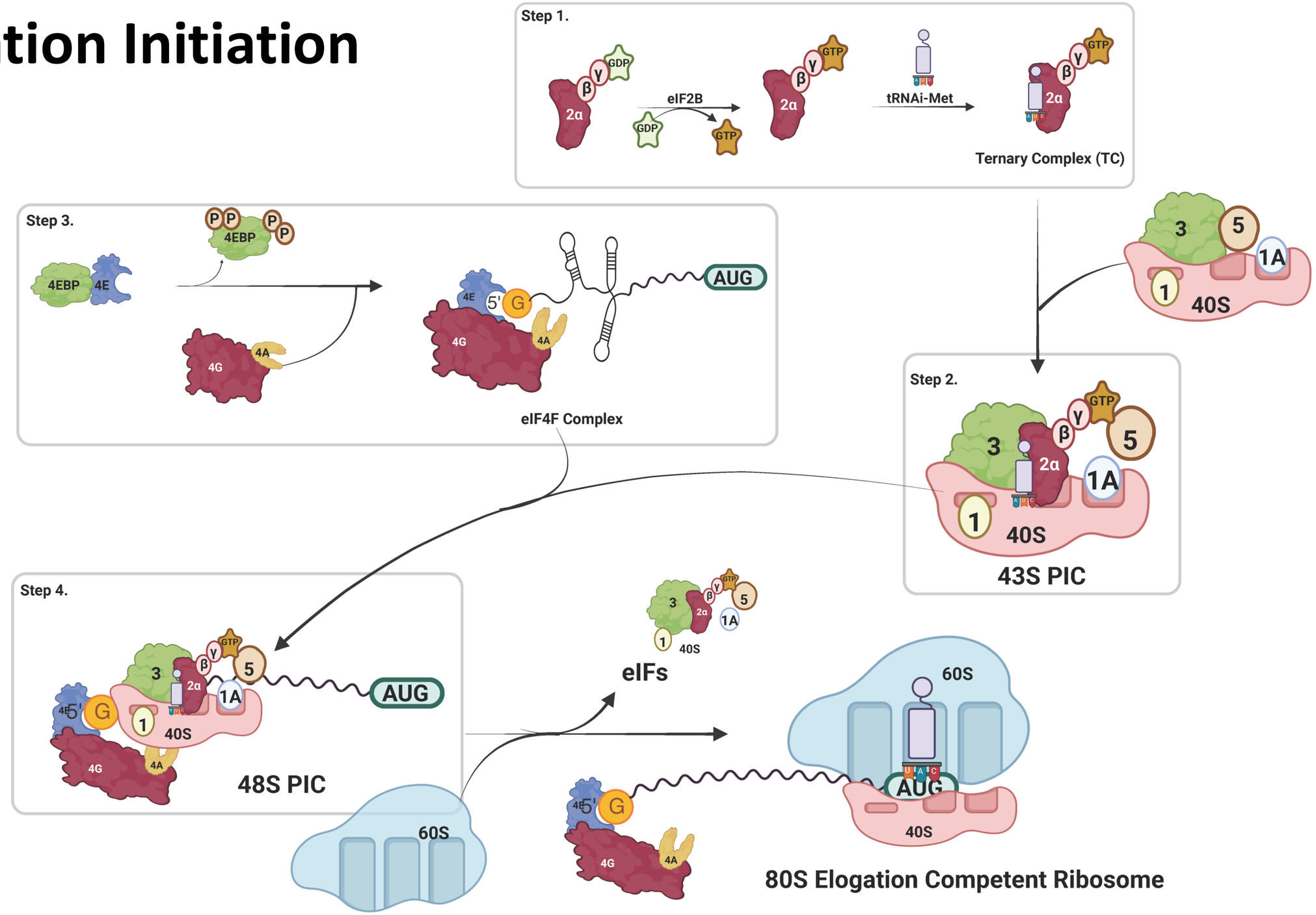
- MYC lacks enzymatic pockets or stable binding sites suitable for small molecules.
- It interacts transiently with DNA and cofactors such as MAX, making direct inhibition challenging.
- MYC is crucial for normal cell growth, so widespread inhibition could cause systemic toxicity.

Therapeutic strategies to target *MYC*-driven tumors.

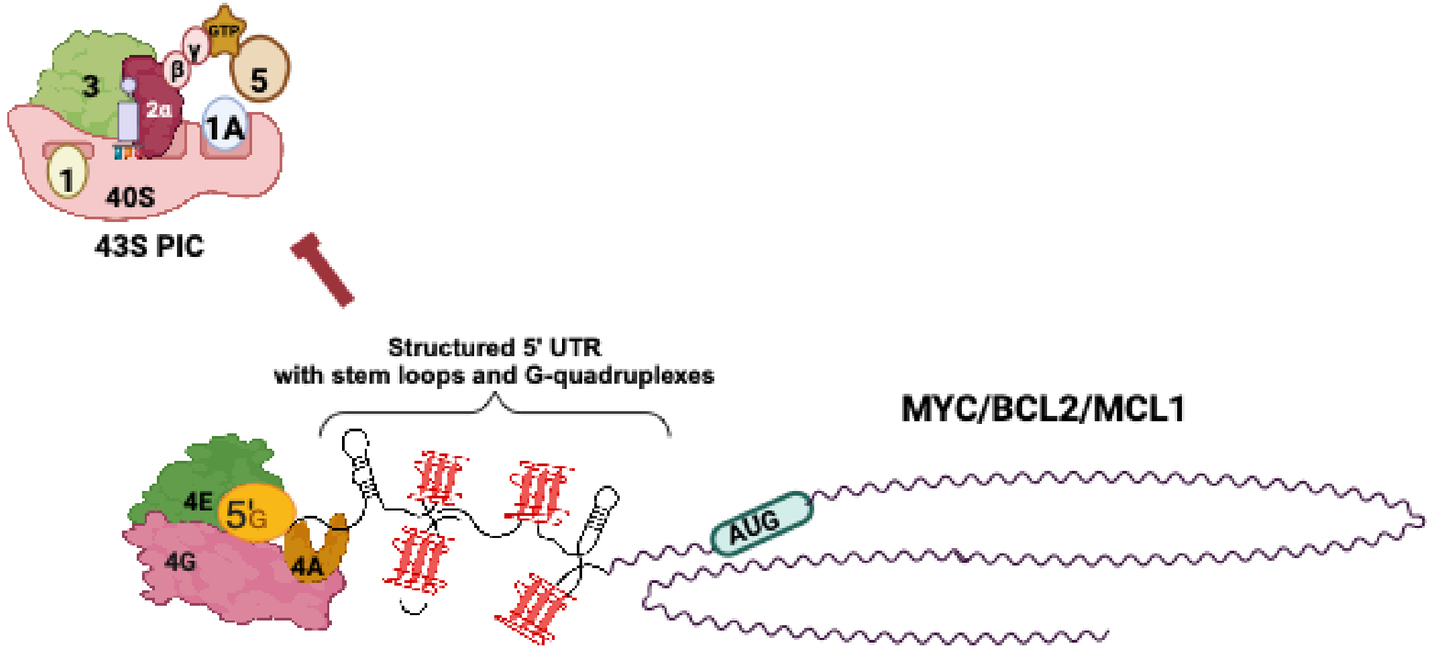


Dhanasekaran R et al. 2022

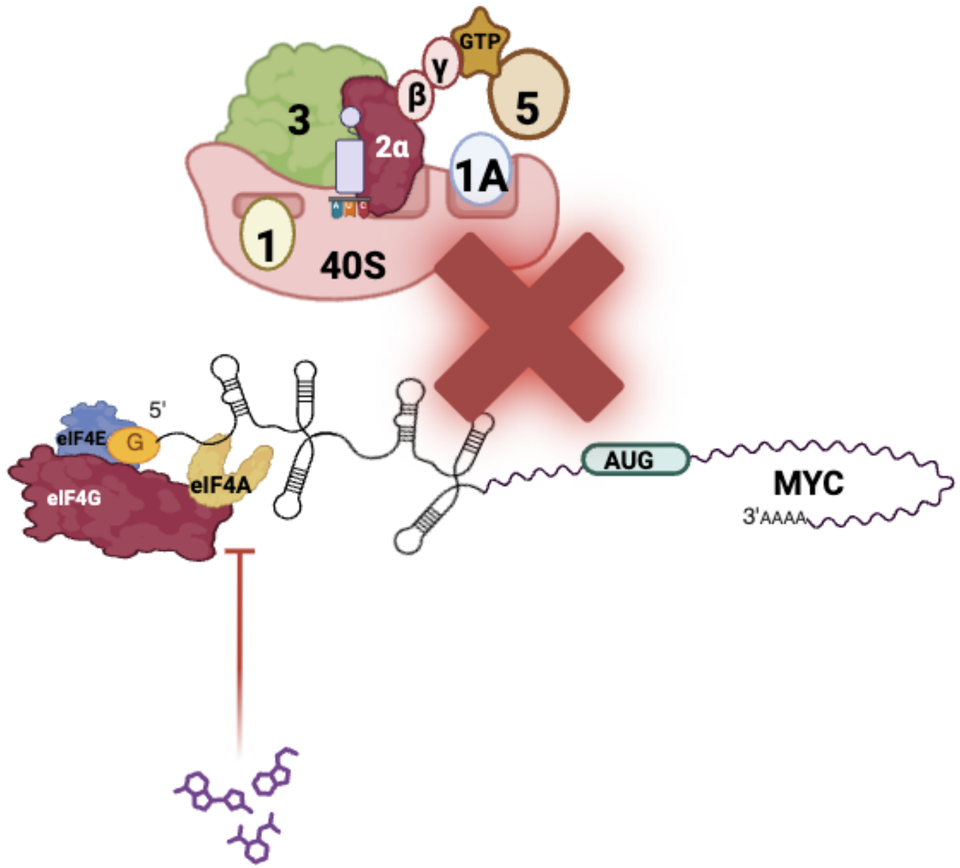
Translation Initiation



eIF4A inhibition is a highly effective, non-genotoxic therapy for MYC-driven Neuroblastoma



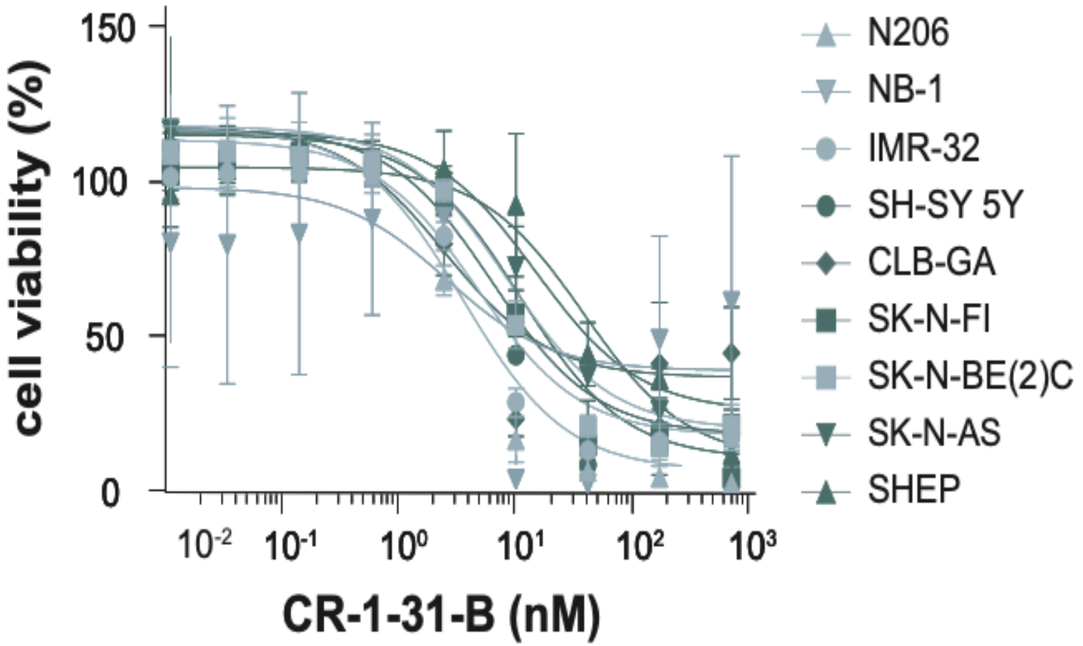
eIF4A inhibitors selectively block MYC protein production and demonstrate potent cancer cell killing *in vitro.*



STRIs: Selective eIF4A (protein biogenesis) inhibitors

- The **short half-life** of MYC makes it **vulnerable to eIF4A inhibition**.
- **Targeting eIF4A** presents a potential treatment approach for MYC-driven cancers.

eIF4A inhibitor targets MYCN-dependent neuroblastoma cells at low nanomolar concentrations.

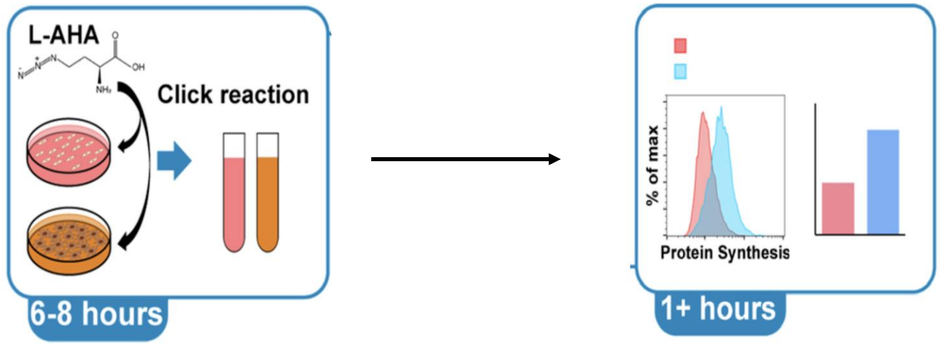


cell line	IC50 (nM, 72h)
CLB-GA	2.455
NB-1	2.66
N206	3.208
IMR-32	3.334
SH-SY-5Y	4.203
SK-N-BE(2)C	5.627
SHEP	14.05

Low nM IC50 confirms the potent killing of NB cells

eIF4A inhibitor confers nascent translation inhibition in NB

Click—it AHA protein synthesis assay



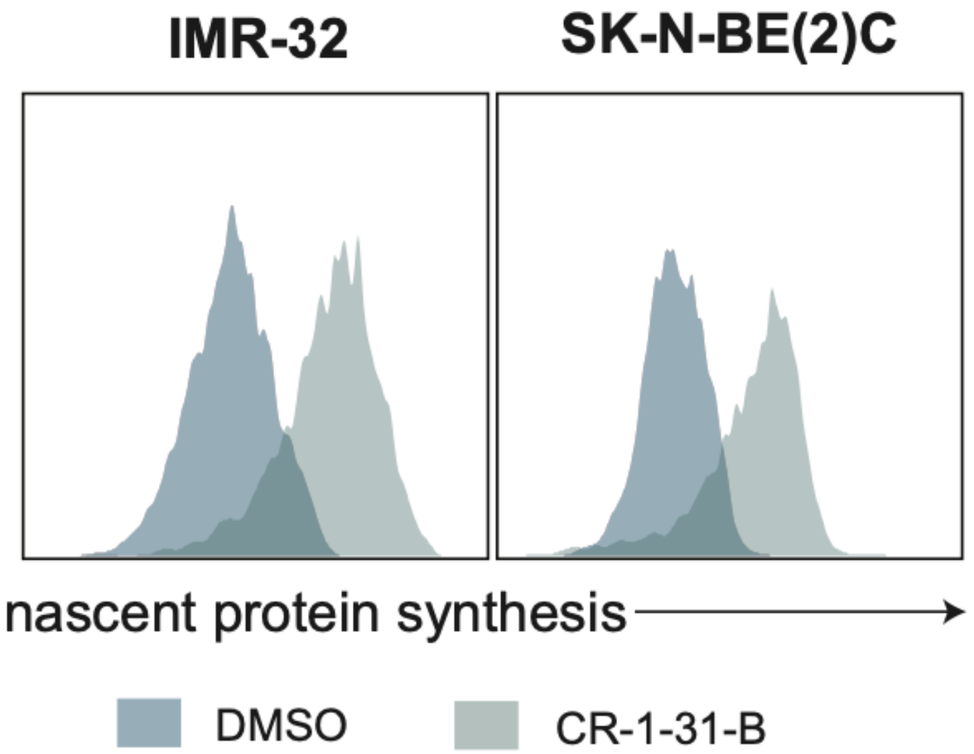
Click Reaction

L-AHA incorporation into the newly synthesized proteins and fluorescent labeling by click chemistry

FACS analysis

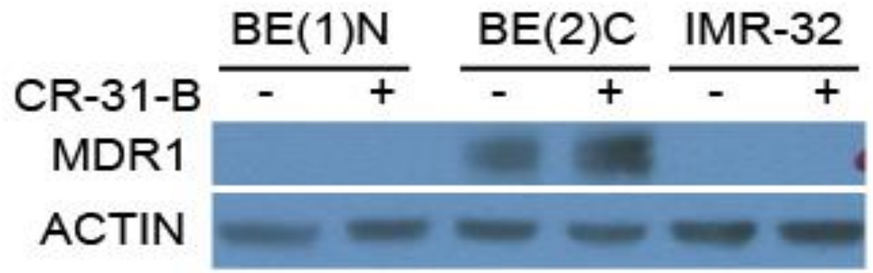
Quantification and statistical analysis of protein synthesis

Nobel Prize in Chemistry:
Carolyn R. Bertozzi, Morten Meldal, and K. Barry Sharpless for the development of click chemistry and bio-orthogonal chemistry

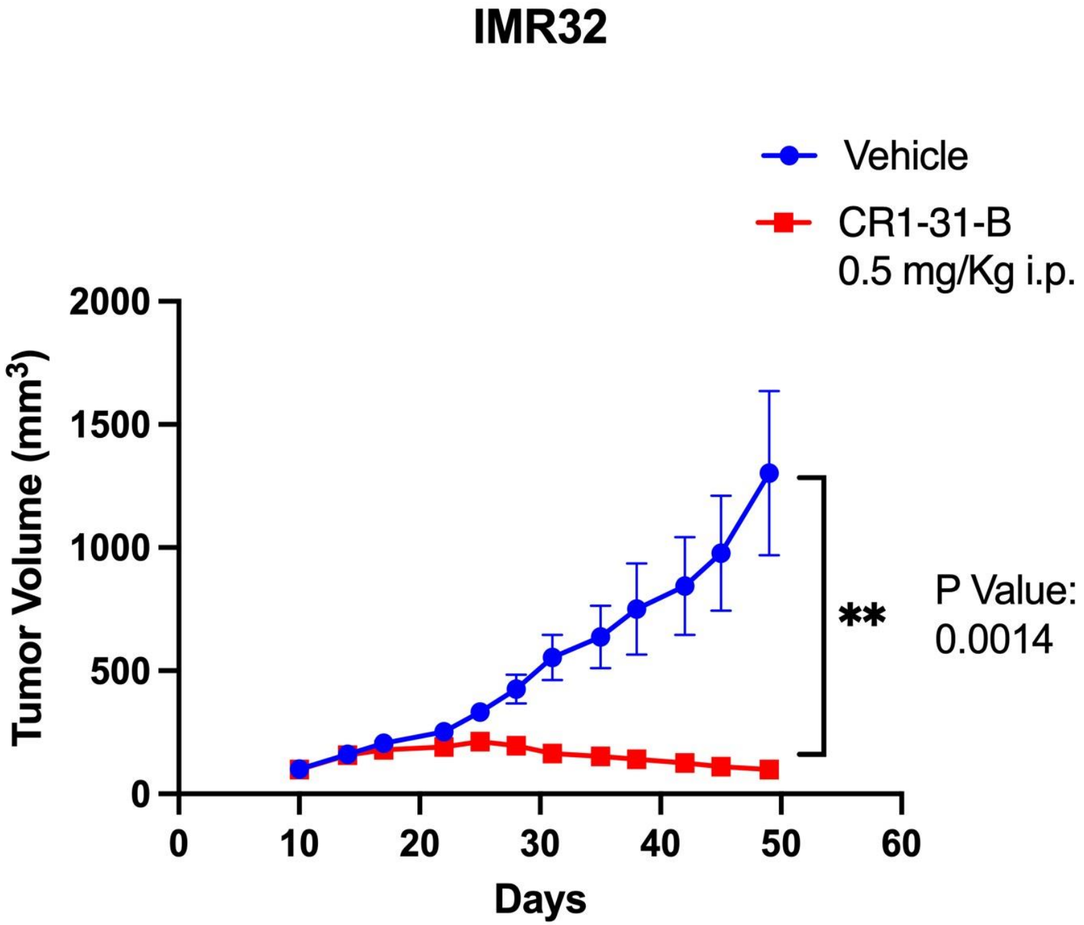


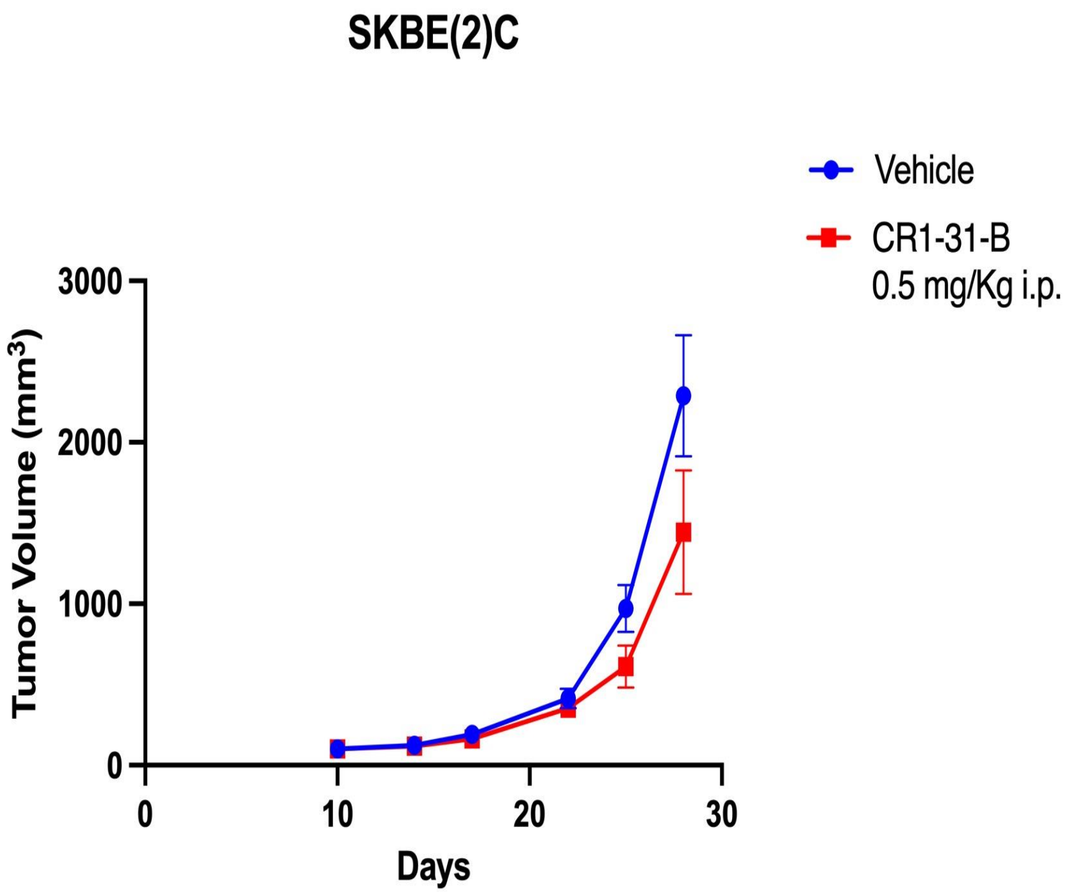
Global Translation is inhibited in multiple NB cell lines

eIF4A inhibitor effectively targets MYCN production in NB but exhibited resistance in the MDR1/PgP expressing NB.



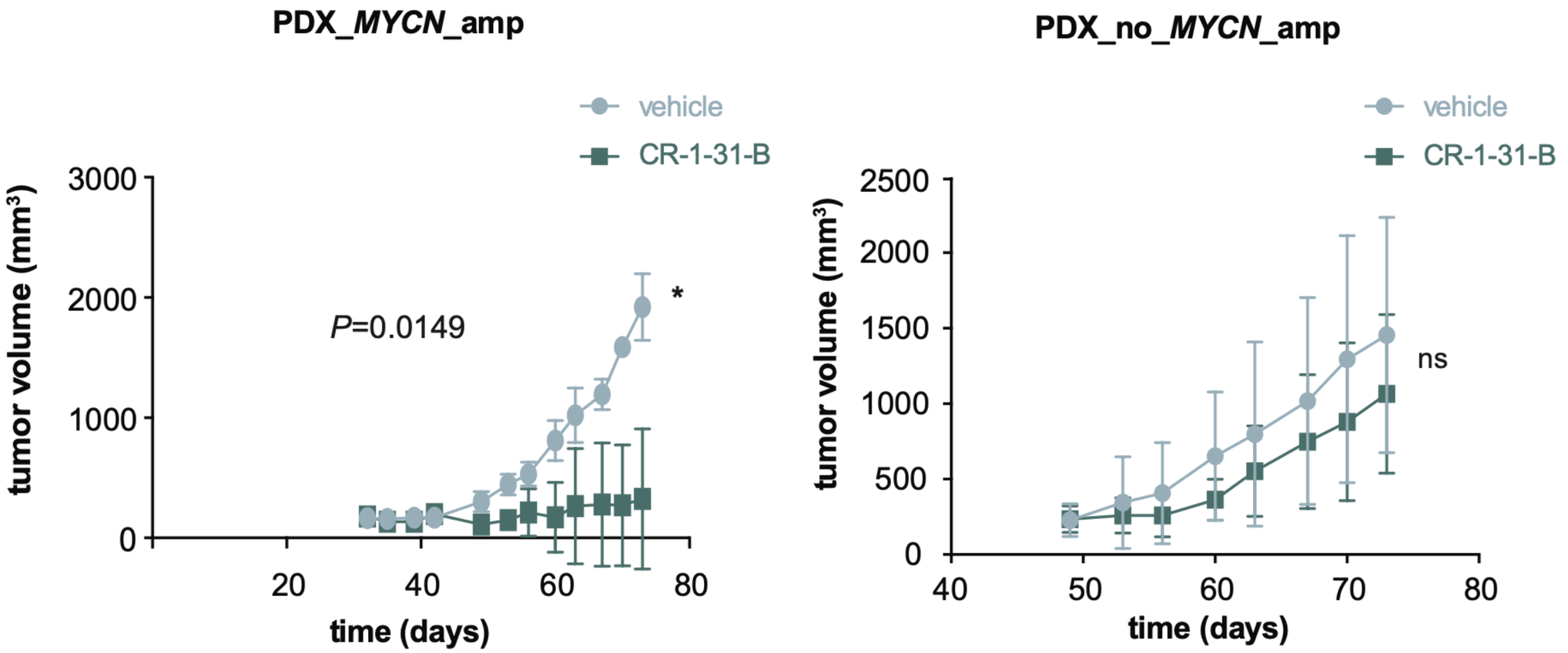
eIF4A inhibitors significantly reduce tumor growth in MYCN-dependent NB, whereas MDR/PgP expression results in resistance.





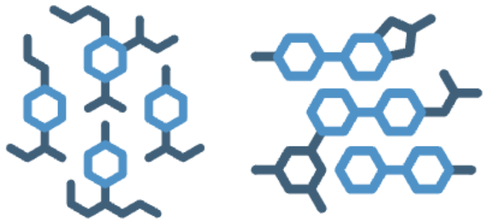
The expression of MDR1/PgP provides resistance to Silvestrol analogs in vivo.

eIF4A inhibitors reduce MYCN-dependent neuroblastoma growth in vivo.

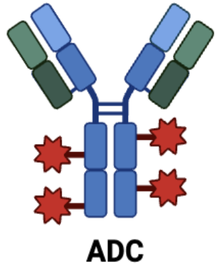


Strategic approaches to target eIF4A in NB

Identifying the lead compounds from a library of eIF4A inhibitors:
Based of on their potency, selectivity, and efficacy in inhibiting MYC protein synthesis

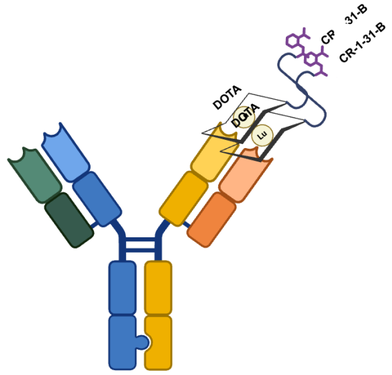


Anti-GD2 linked with eIF4A inhibitor:
Direct linking the eIF4A inhibitor to the anti-GD2 for target specific delivery



ADC

Bispecific anti-GD2 and anti-DOTA recognising eIF4A linked to DOTA:
targeted delivery of multiple molecules of drug to the cancer site.



Debate/Discussion

Topics are listed below.

1. Cancer is a disease of development gone wrong.

2. We should repurpose developmental drugs for oncology.

3. Targeting developmental pathways is too risky because of their role in normal tissue homeostasis.

4. Ethical boundaries in targeting developmental pathways in pediatric cancers.

5. Transcription factors like MYC and TWIST are undruggable — and will remain so