NEW APPROACHES TO INVESTIGATE NOVEL AGENTS IN EWING SARCOMA

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ABOUT EWS

- It is an aggressive cancer of the bone and soft tissue with the peak incidence at 15-years old
- The systemic chemotherapy has a major impact on survival
- Outcomes of metastatic EWS is poor.
- Late effects of intensification therapy for improving survival include: infertility, cardiotoxicity, secondary malignancy

STANDARD CHEMOTHERAPY

- Vincristine + Doxorubicin + Cyclophosphamide (VDC) / IE for 12 weeks (6 cycles) of induction given every 2 weeks
- Consolidation include 22 weeks (12 cycles) VDC / IE / VC.
- **COG trial AEWS1031** evaluated the use of alternating VDC (2 cycles), IE (2 cycles), VCR + Topotecan + cyclophosphamide (VTC, 2 cycles) in induction
- In **COG trial AEWS1031**, consolidation includes 22 weeks of VTC / IE / VDC

NOVEL AGENTS FOR EWS

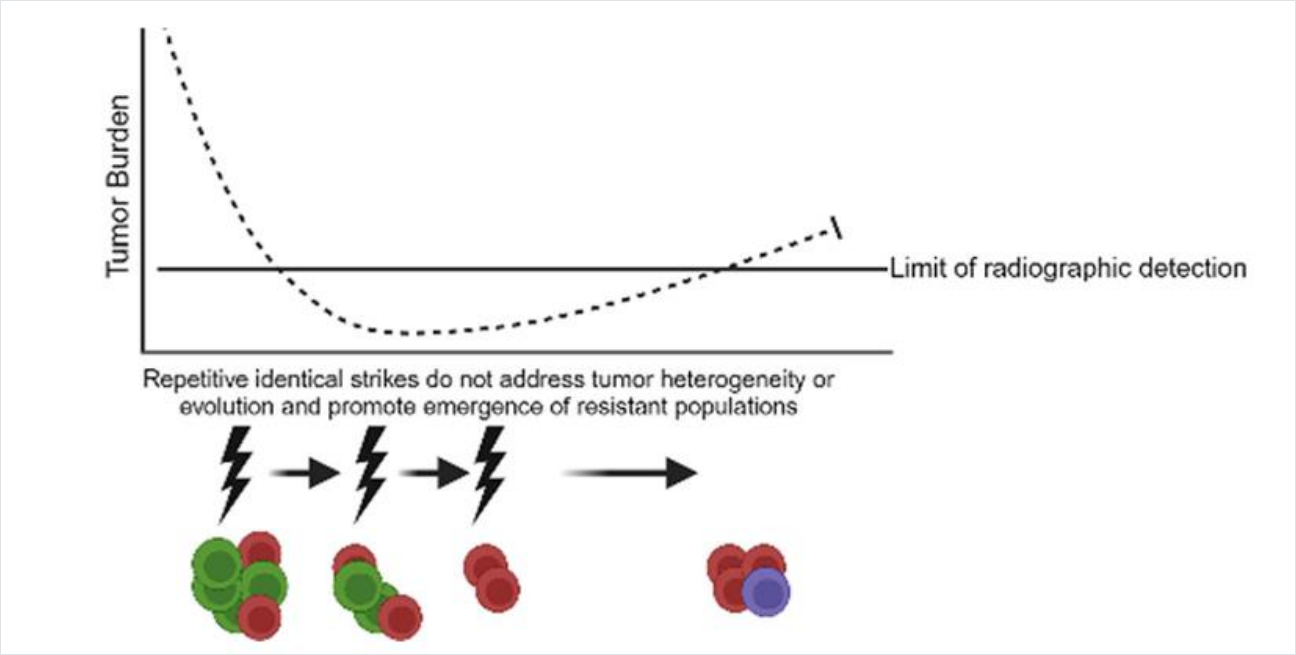
Evaluation the priority and effects of novel agents in treating EWS is important for decreasing the late effects and increasing the survival rates

WHAT IS THE PROBLEM IN APPROACHES?

- The dose intense VDC/IE is effective in reducing the population of tumor large cells (first-strike)
- But, EWS is a chemotherapy sensitive disease with tumor heterogeneity

- Repetitive first-strike therapy can not affect totally and there will be resistant subclones of tumor cells

WHAT IS THE PROBLEM IN APPROACHES?



PROBLEMS IN RELAPSED EWS

- Single agent therapy in relapsed EWS has a low EFS (nearly 12.7%)
- Clinical trials showed Ifos could not be the most active agent in the first relapse
- Trial designs about multiple agents will be useful in evaluating the efficacy of novel agents by a framework of first and second-strikes.

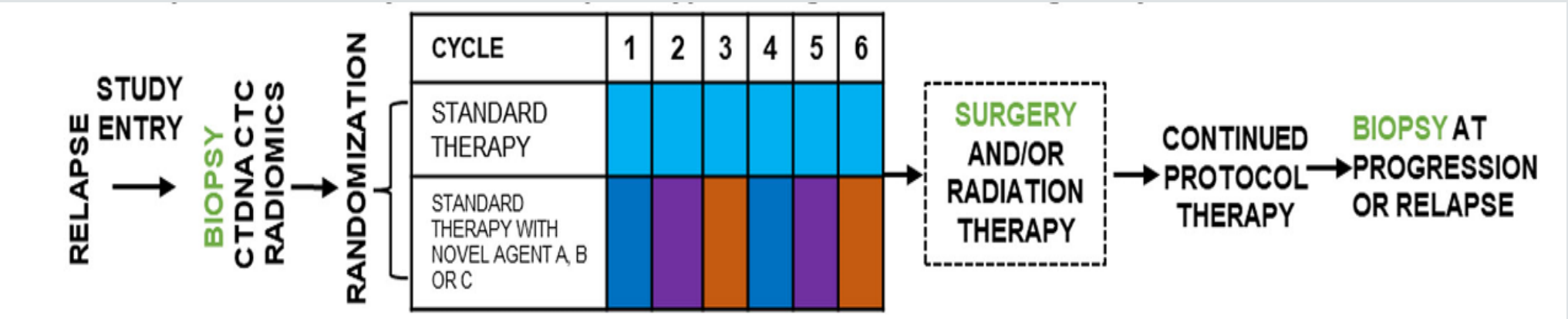
FIRST & SECOND-STRIKE THERAPIES

- The first-strike therapy (intensive therapy) dramatically decrease without eradicating tumor cells
- The second-strike therapy target residual tumor cells.
- Combination of agents are novel therapy in high-risk population which can affect on heterogenous tumor cells

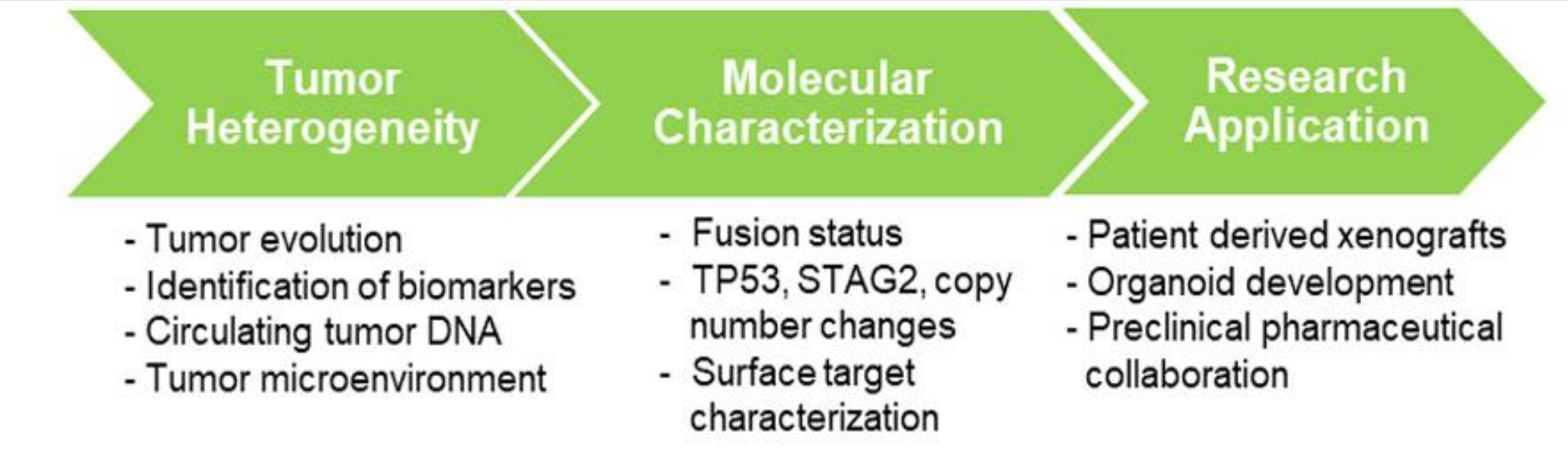
DISEASE SITE-DIRECTED THERAPY

- Disease directed-therapy is effective in relapsed/refractory EWS.
- The use of surgery and/or radiotherapy with systemic chemotherapy is necessary in this framework
- In this therapy, EWS biology is needed which will be done on ctDNA of tumor samples for evaluating the tumor heterogeneity
- Multi omics evaluation will provide information about tumor resistance to agents

DISEASE SITE-DIRECTED THERAPY



ANALYSIS OF BIOPSIES' SAMPLES



NOVEL THERAPY IN EWS

Oncoprotein targeting

Epigenetic inhibition

Immunotherapy

TIME

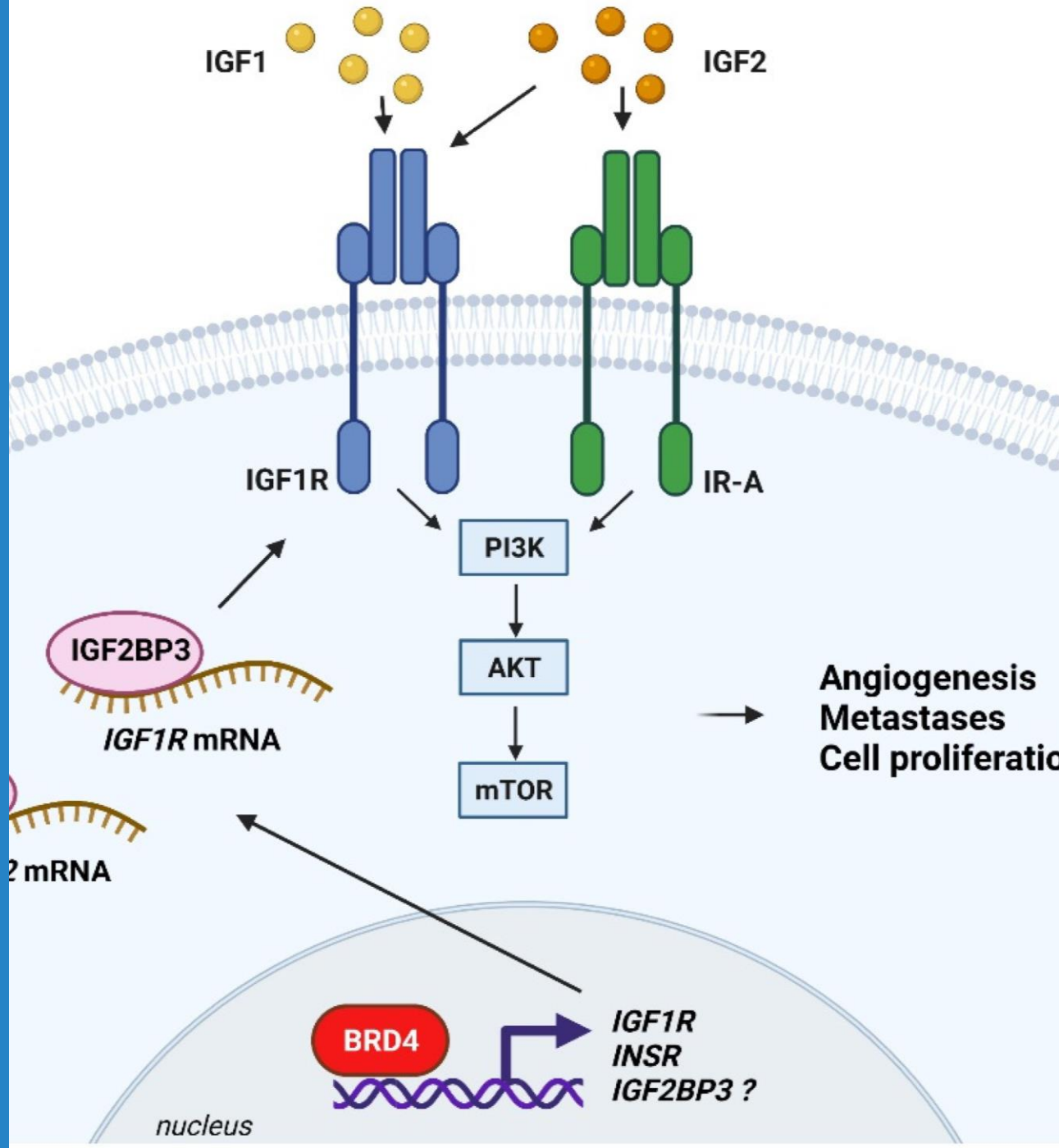
Improving cytotoxic chemotherapy

Increased replication stress

WNT pathway inhibition

Receptor tyrosine kinase pathway

Targeting tumor metabolism



ONCOPROTEIN IN EWS

- One of the characterizations in EWS is recurrent translocations between FET and ETS protein families
- The most common oncoprotein translocation is: EWSR1:FLI1 (t(11;22))
- It is an aberrant transcriptional factor

NOVEL THERAPIES SHOULD TARGET ONCOPROTEIN EWSR1:FLI1

Targeting this fusion oncoprotein include inhibiting its transcriptional program and blocking proteins for regulating its function

THE AGENT FOR ONCOPROTEIN TARGETING:

TRABECTEDIN

- Binds to the minor groove of DNA for inhibiting EWSR1:FLI1 function
- Generate DNA damage
- Sensitize EWS cells to Irinotecan

THE AGENT FOR ONCOPROTEIN TARGETING:

LUBRINECTEDIN

- It is the next generation analog of Trabectedin
- Has improved safety index
- It is under investigation in relapsed EWS
- It is under evaluation in combination with Irinotecan in adults

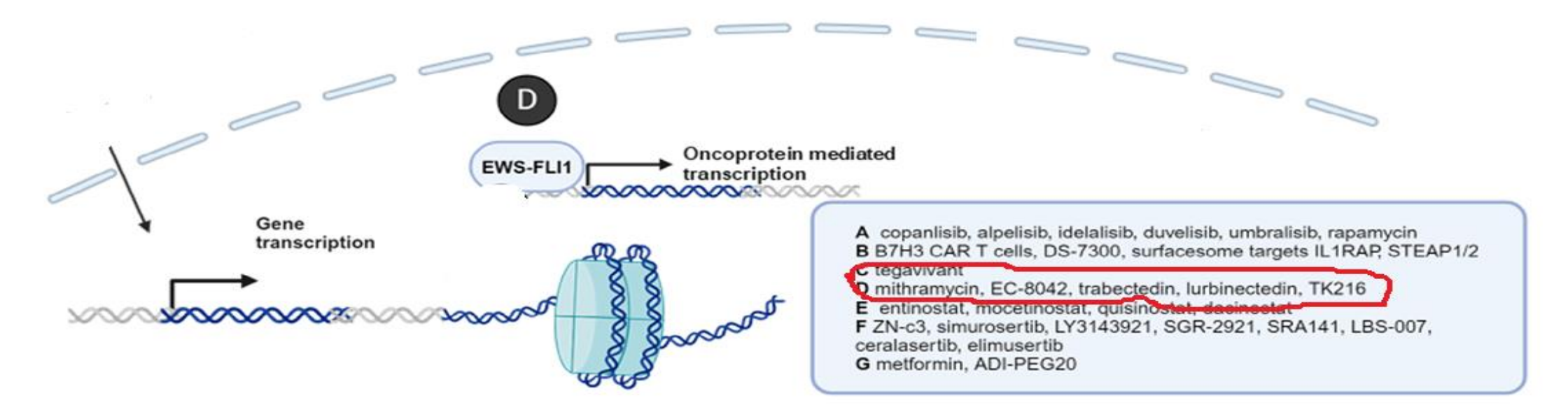
THE AGENT FOR ONCOPROTEIN TARGETING: **MITHRAMYCIN**

- A small molecule which blocks RNA helicase to bind to EWSR1:FLI1and makes apoptosis in EWS cells is:YK-4-279
- Mithramycin is the analog ofYK-4-279 that reverse the transcriptional program of EWSR1:FLI1
- There are some reports of hepatotoxicity with Mithramycin in relapsed/refractory EWS

SUMMARY OF AGENTS WITH ONCOPROTEIN TARGETING

Drug name(s)	Mechanisms	Strategy	Phase of testing
TK216 [33, 35]	Inhibition of RNA Helicase A binding with FLI1	Targeting the oncoprotein	Phase I/II trial completed
Trabactedin [25, 26], Lurbinectedin [29]	EWS::FLI1 transcriptional program	Targeting the oncoprotein	Phase I/II trial completed
Mithramycin, EC-8042 [36–38]	EWS::FLI1 transcriptional program	Targeting the oncoprotein	Phase I/II trial completed

SUMMARY OF
AGENTS WITH ONCOPROTEIN TARGETING



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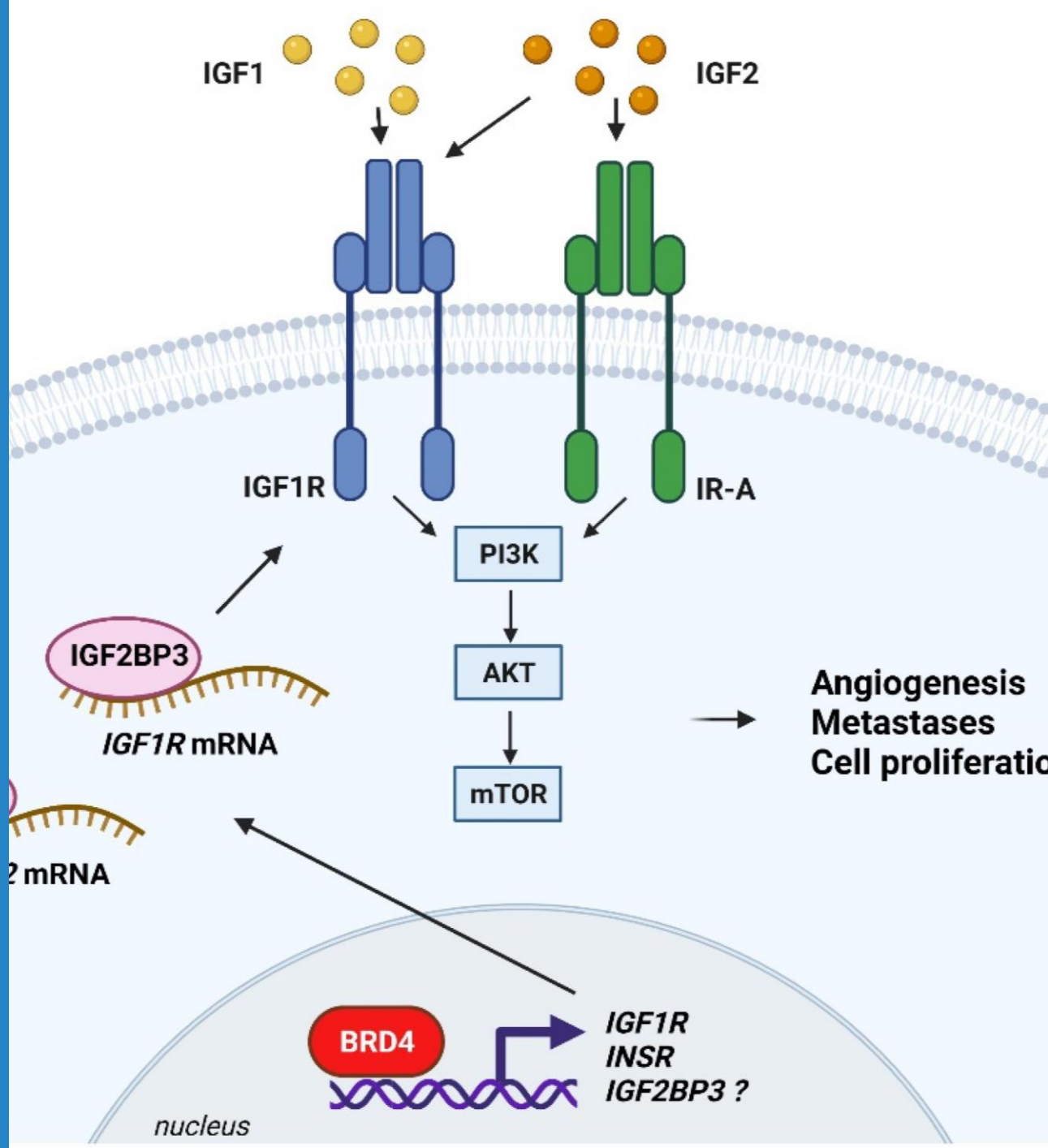


EPIGENETIC IN EWS

- There are few somatic mutations in EWS
- Epigenetic makes these somatic mutation to tumor development and progression through NuRD complex
- LSD1 as a cofactor interact with NuRD complex for gene expression and LSD1 is over expressed in patients with EWS
- t(11;22) in patients with EWS will suppress tumor suppressor genes and will do this process by LSD1 and NuRD complex

NuRD complex = Nucleosome Remodeling and Deacetylase complex

LSD1 = Lysine-specific Demethylase-1

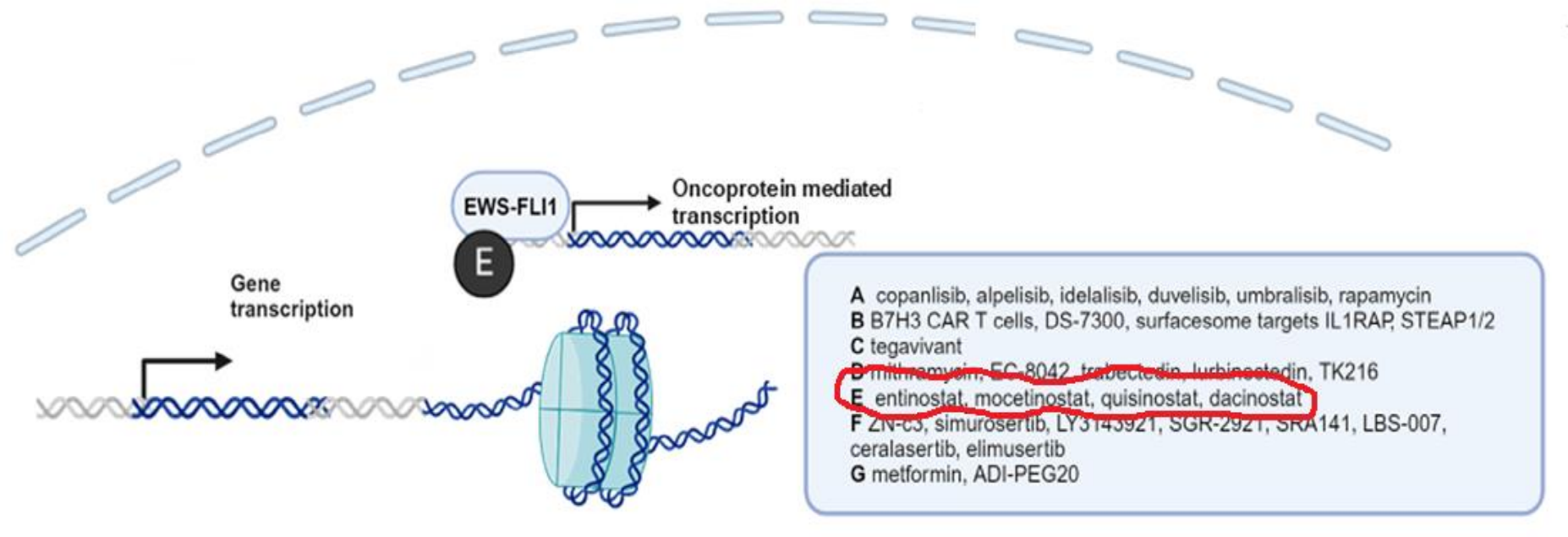
NOVEL THERAPIES SHOULD BLOCK LSD-1 (LSD-1 INHIBITOR AGENTS)

Blocking LSD-1 will interrupt the function of EWSR1-FLI1 and will induce apoptosis

THE AGENT FOR EPIGENETIC INHIBITION

- Entinostat
- Mocetinostat
- Quisinostat
- Dacinostat

SUMMARY OF
AGENTS WITH GENETIC INHIBITION



SUMMARY OF AGENTS WITH GENETIC INHIBITION

Entinostat, mocetinostat, quisinostat, dacinostat [45–59]	Histone deacetylase	Epigenetic inhibition	Phase I trial completed

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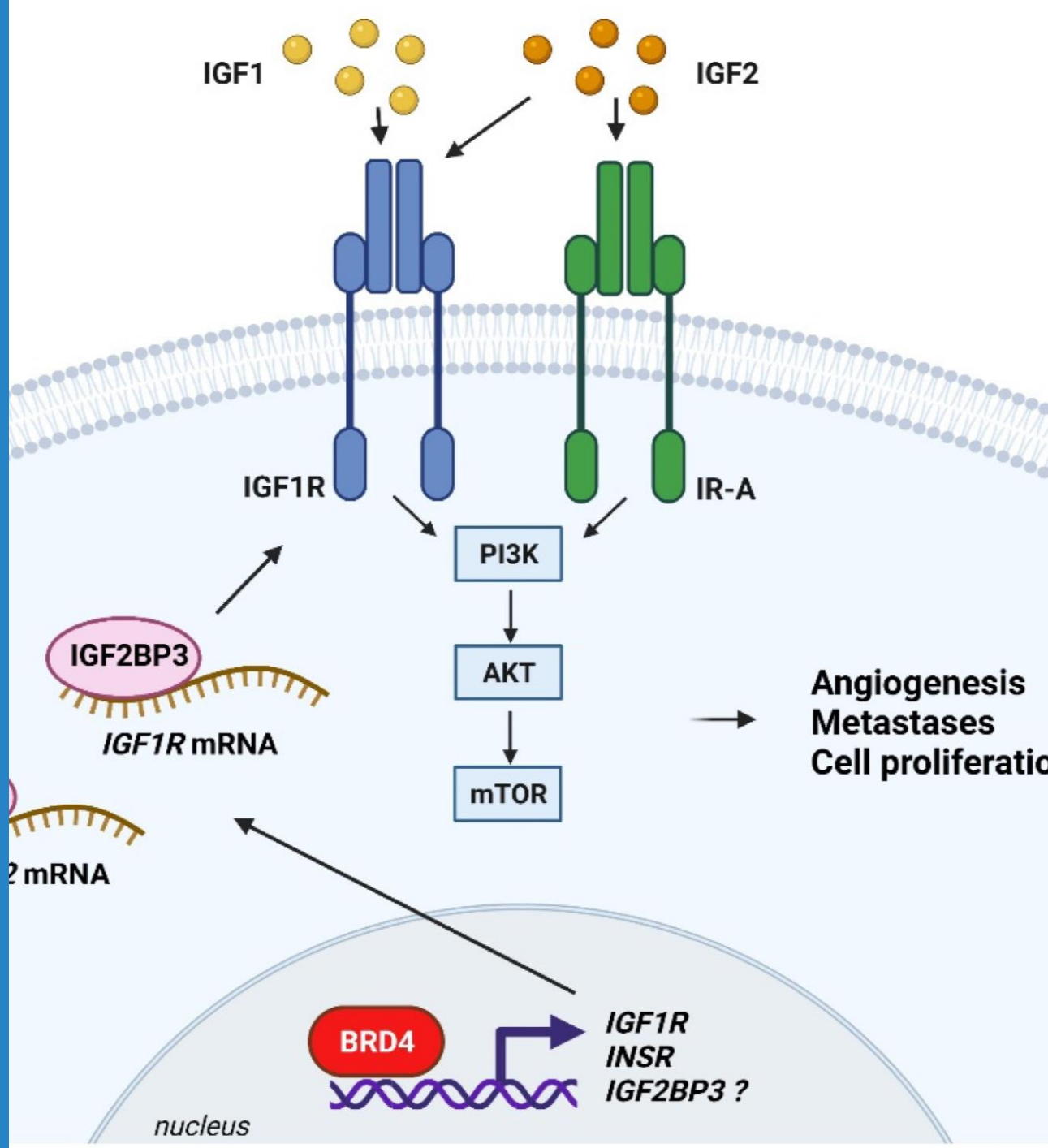
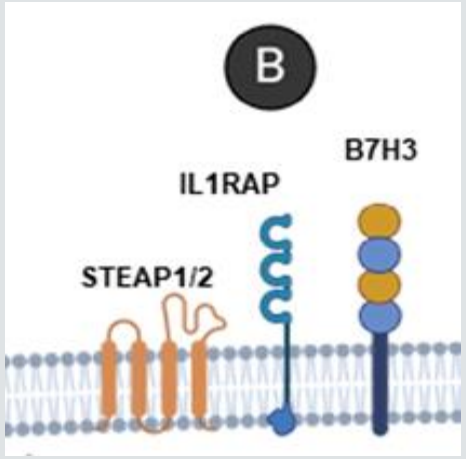
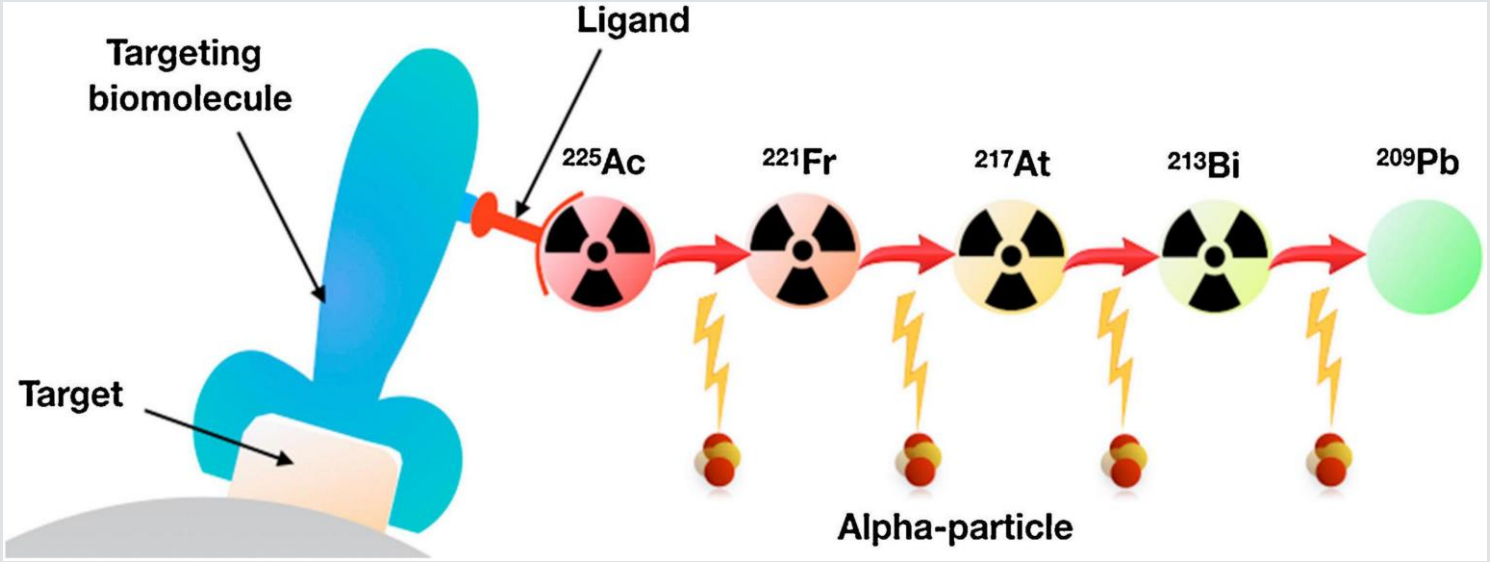


CELL SURFACE PROTEINS IN EWS

- Cell Surface Proteins are: STEAP1, ADGRG2, ENPP1, CDH11
- Immunotherapeutic cellular therapy can target these proteins
- Tumor targeted radiopharmaceutical like TAT (targeted alpha particle therapy)
- In this way, antigen expression in resistant cells are important



TAT


Ligand
Targeting biomolecule
225Ac
221Fr
217At
213Bi
209Pb
Target
Alpha-particle

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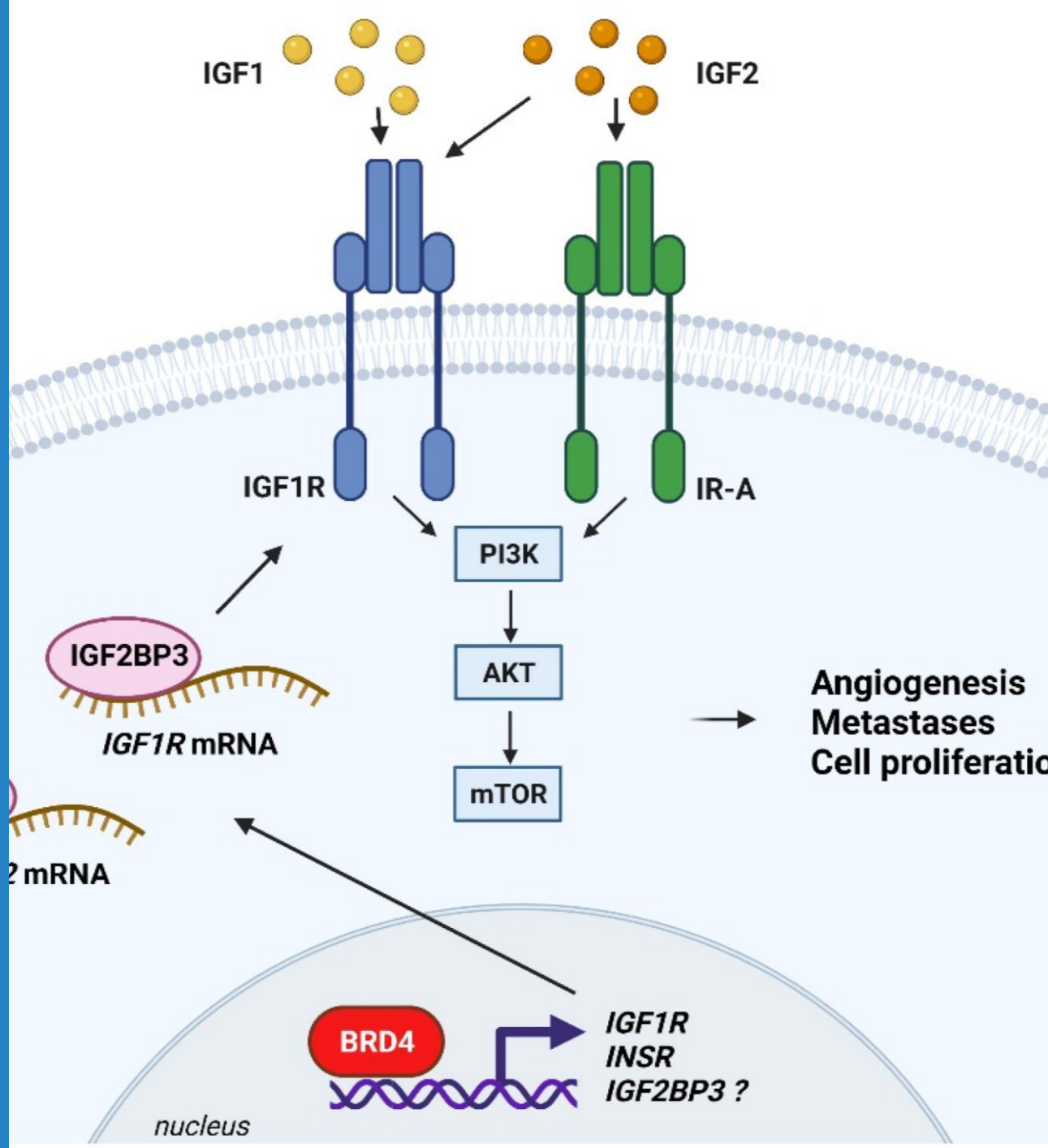

TIME IN RELAPSED EWS

- Tumor Immune Micro Environement
- Including through targeting the immune cells in the relapsed patients with EWS
- PD-1 is a target for cancer immunotherapy that works by blocking immune system
- Some studies showed that PD-1 targeting is effective in relapses EWS

THE AGENT FOR PD-1 TARGETING:

PEMBROLIZUMAB

- A tested single agent
- It is a checkpoint inhibitor targeting the PD-1
- Combination of Trabectedin and Pembrolizumab can induce apoptosis and immune checkpoint blockade

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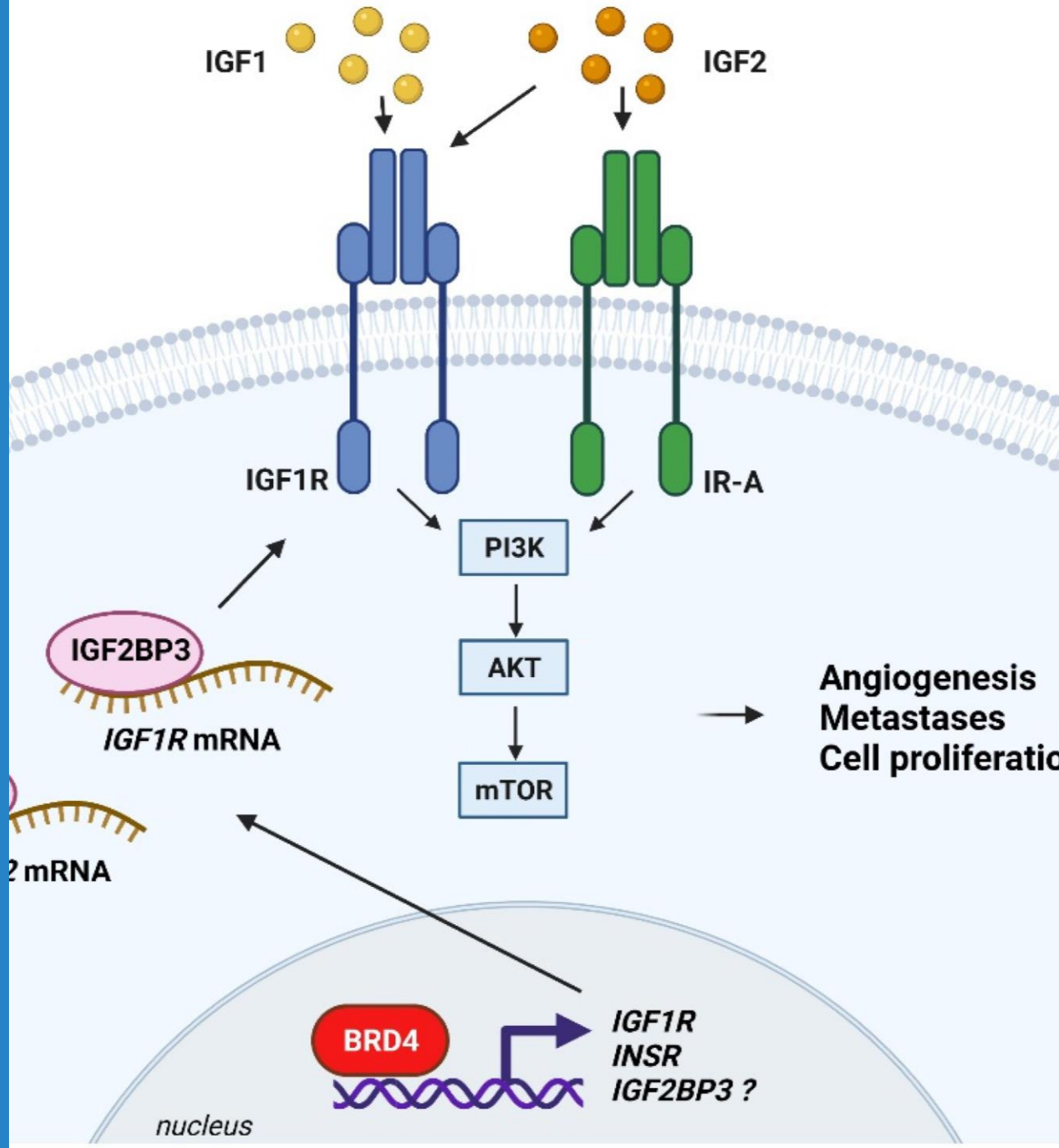
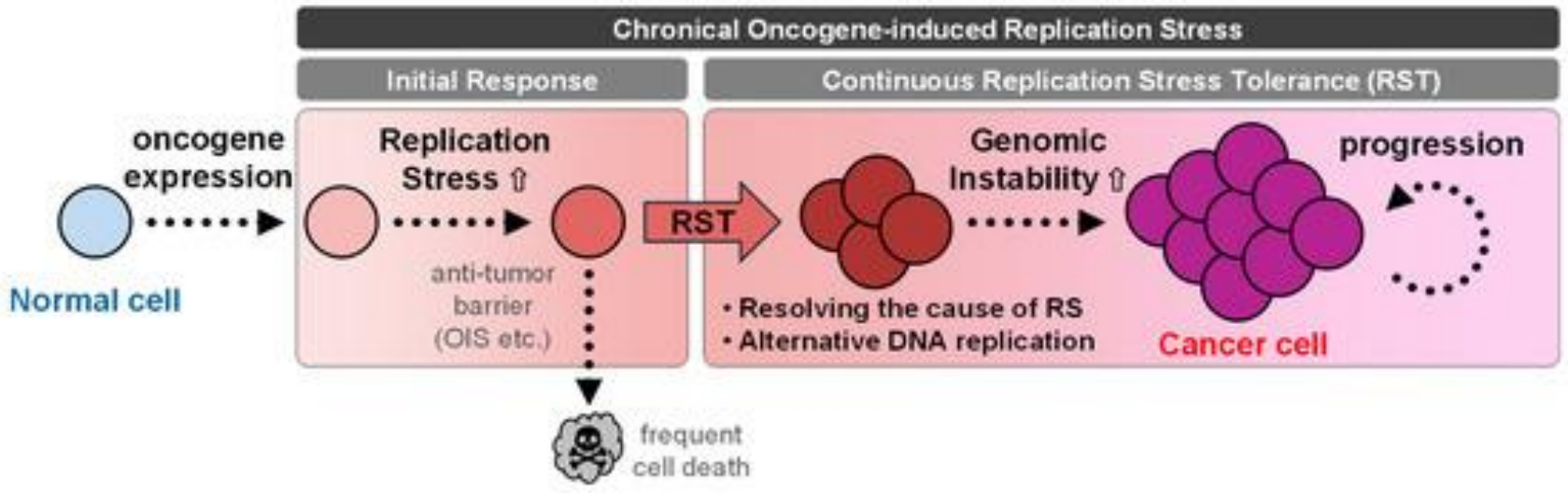


CYTOTOXIC CHEMOTHERAPY IN EWS

- At the initial time of diagnosis, EWS is responsive to chemotherapy specially in induction phase
- Replication stress is a major cause of genome instability in cancer cells
- Deregulation of DNA replication is replication stress that can alter the responses to the treatment

REPLICATION STRESS



CYTOTOXIC AGENTS

Cytotoxic agents and targeted replication stress are the main idea to improve the response to chemotherapy, reduce toxicity to non-tumor tissues and inhibit drug resistance

DOXIL

- It is a pegylated liposomal formulation of Doxorubicin
- It was tested as a single agent
- It was tested in combination with VCR and CPA in relapsed solid tumors

INFINATAMAB DERUXTECAN

- It is an experimental anticancer treatment which is developed by MERCK
- It is a monoclonal antibody which links to topoisomerase I

LIPOSOMAL IRINOTECAN

- It has active metabolites including nanoparticle and drug conjugate formulation
- It is as an active agent in the standard therapy for relapsed EWS
- There are two trials for specific Irinotecan in EWS for evaluating the tolerability, improving the penetration in bones and increasing the quality of life

SUMMARY OF IMPROVING CYTOTOXIC CHEMOTHERAPY

B7H3 CAR T cells, infinatamab deruxtecan [64, 79, 80], vobramitamab, duocarmazine	B7H3	Targeting the surfacesome	Phase 1 trial ongoing
Liposomal doxorubicin, liposomal irinotecan, LMP400, PEP02 [73–77]	Nanoparticle, liposomal delivery	Improving tumor delivery of existing agents	Phase I/II trials completed/ongoing

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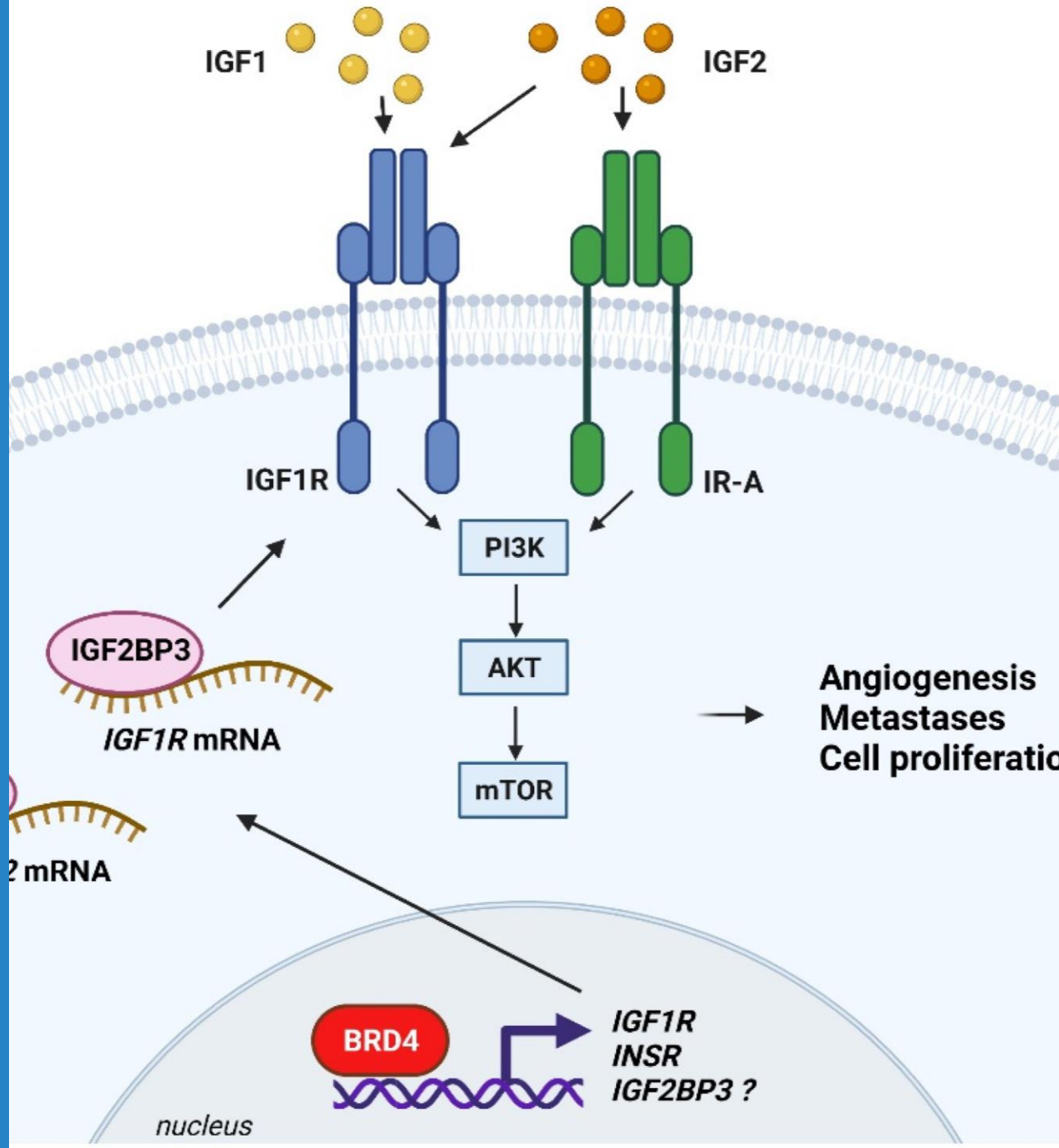

INCREASED REPLICATION STRESS

- Cytotoxic chemotherapy can affect replication stress in EWS
- In normal cells, there are PARP which is a protein help damage cells to repair themselves
- In cancer cells, there are PARP inhibitors which inhibit the normal action of PARP
- In EWS, PARP inhibitors are highly active and during chemotherapy and other therapies can induce replication stress in the cells

REPLICATION STRESS

Replication stress is an attractive strategy and modern therapy through binding targeted agents, single agents and drug deliveries which are under research in pediatric population

SUMMARY OF AGENTS FOR REPLICATION STRESS

Simurosertib, LY3143921, SGR-2921, ZN-c3, Ceralasertib, elimusertib, Olaparib, talazoparib [89–107]	DDK, WEE1, ATR, PARP	Replication stress	Phase I/II trials completed, ongoing preclinical evaluation

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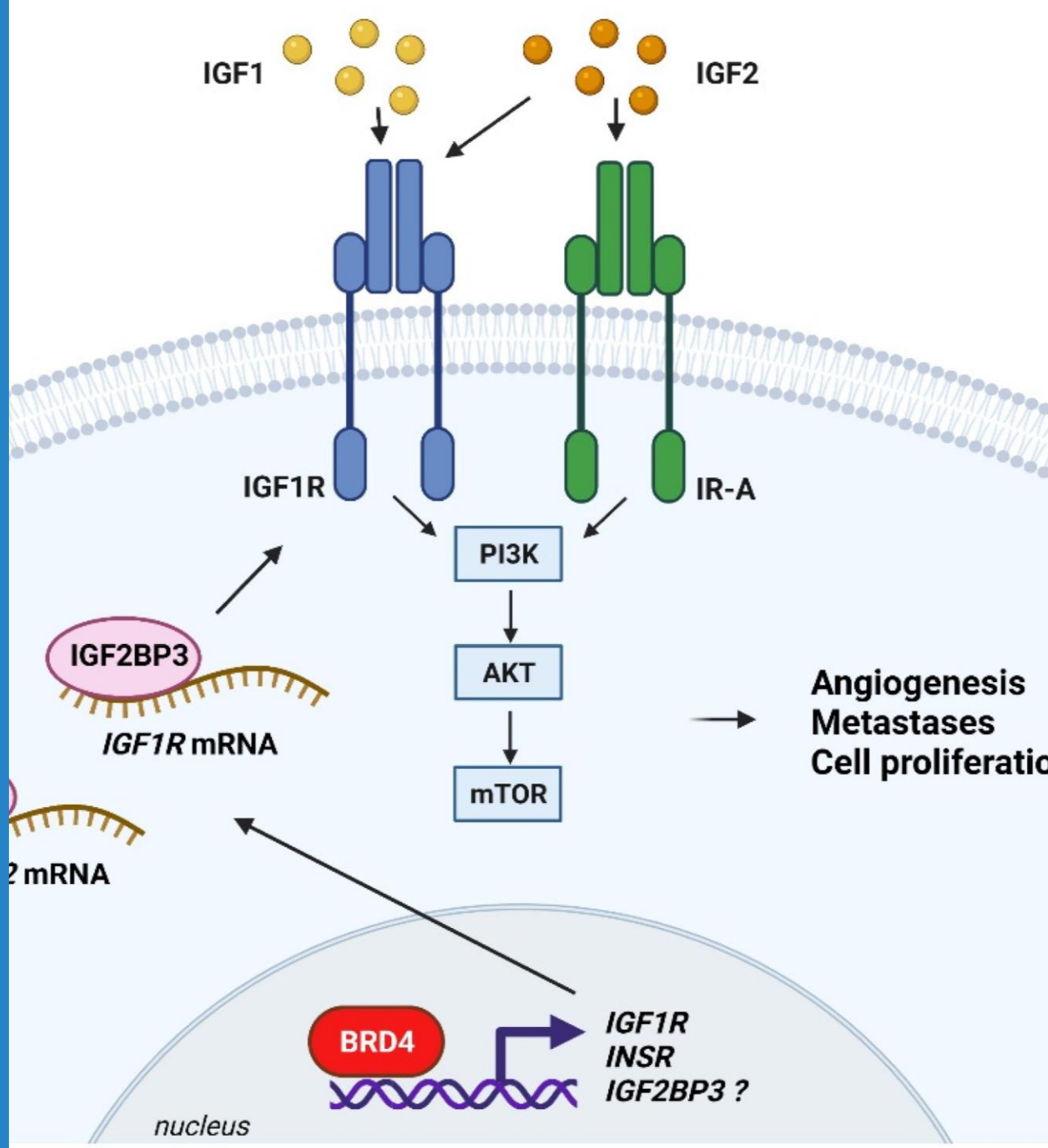

WNT PATHWAY INHIBITION IN EWS

- WNT pathway has a key role in bone development and activating mutations
- It has potential role in tumorigenesis and survival
- Activating the WNT signals can make cytoskeletal changes and metastasis
- WNT signal has crosstalk with TGF-β pathway in the skeletal development and tumor behavior
- Targeting this crosstalk can prevent metastasis too.

AGENT FOR WNT PATHWAY INHIBITION: **TEGAVIVINT**

- It is a first-in-class WNT pathway inhibitor that disrupts a critical interaction with β-catenin and degrade it
- WNT/ β-catenin has a pro angiogenesis and metastatic phenotype
- This agent can prevent initial relapse or metastasis

SUMMARY OF TEGAVIVINT

Tegavivant [113–118]	Wnt pathway	Prevention of metastases development	Phase I/II studying ongoing

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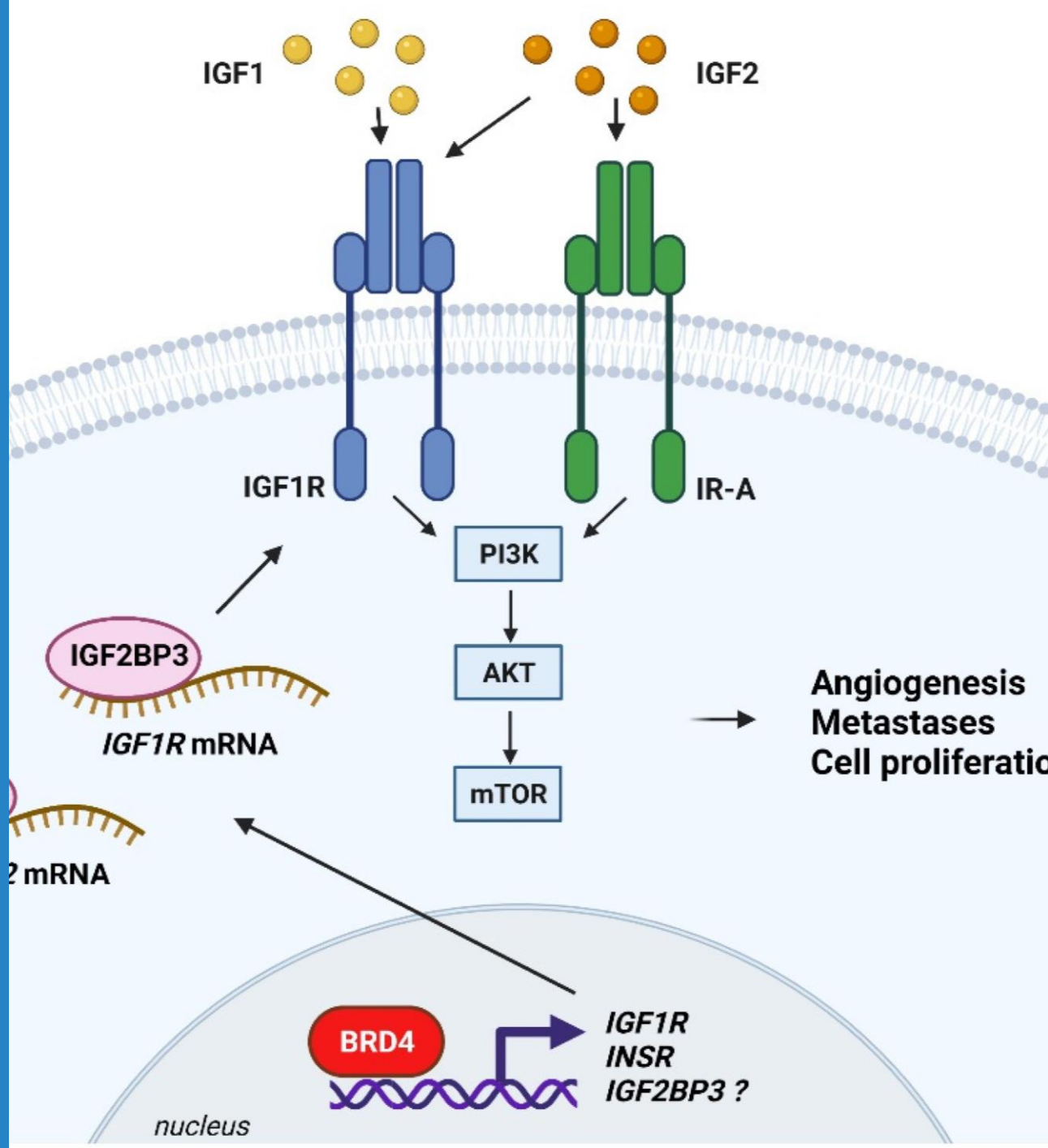

RECEPTOR TYROSINE KINASE PATHWAY

- This receptor regulates cellular growth, differentiation and apoptosis.
- In EWS patients, this receptor dysregulates with overexpression or deactivation
- Multiple tyrosine kinase inhibitors which lead to angiogenesis are like:

➢ VEGFR, Stem-cell factor receptor, MET, RET

RECEPTOR TYROSINE KINASE INHIBITOR: REGORAFENIB

- It is a tyrosine kinase inhibitor which target VEGFR, RET and KIT
- It is studying as a prospective trial in metastatic EWS
- It blocks tyrosine kinases that are very active in angiogenesis, cancer development and growth, and maintenance of the tumor microenvironment.

RECEPTOR TYROSINE KINASE INHIBITOR: CABOZANITIB

- It targets VEGFR2, RET and KIT
- It has efficacy as a single agent in relapsed EWS
- It can use in combination with chemotherapy as a maintenance therapy

SUMMARY OF TKI

Cabozantinib, regorafenib [125, 132]	Tyroskine kinase inhibitor	Inhibit VEGFR, RET, KIT, MET	Phase I/II trials completed, phase III trials planned

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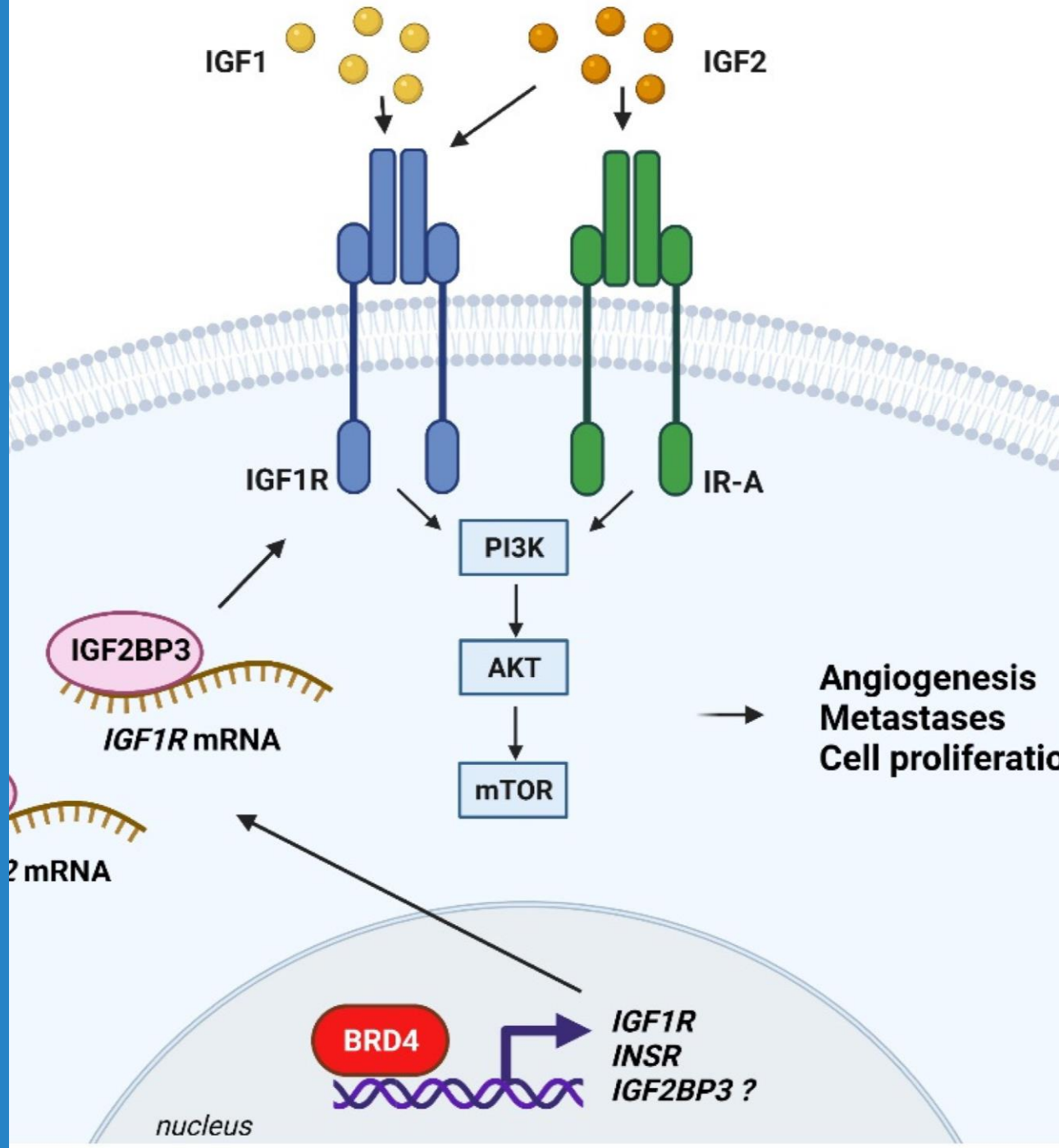


TARGETING TUMOR METABOLISM

- Metabolism in cancer cells are different from normal cells which depend to the heterogeneity of the tumor
- Pathways involved to Glucose metabolism are important in EWS cell growth and survival, because EWS cell lines are highly glycolytic
- Patients with EWS:FLI1 have overexpression of lactate dehydrogenase A (LDHA) which is in the glucose pathway

INHIBITING TUMOR METABOLISM THROUGH

Agents that can affect on the Glucose or Lipid pathways can

alter in the metabolism and growth cancer cells

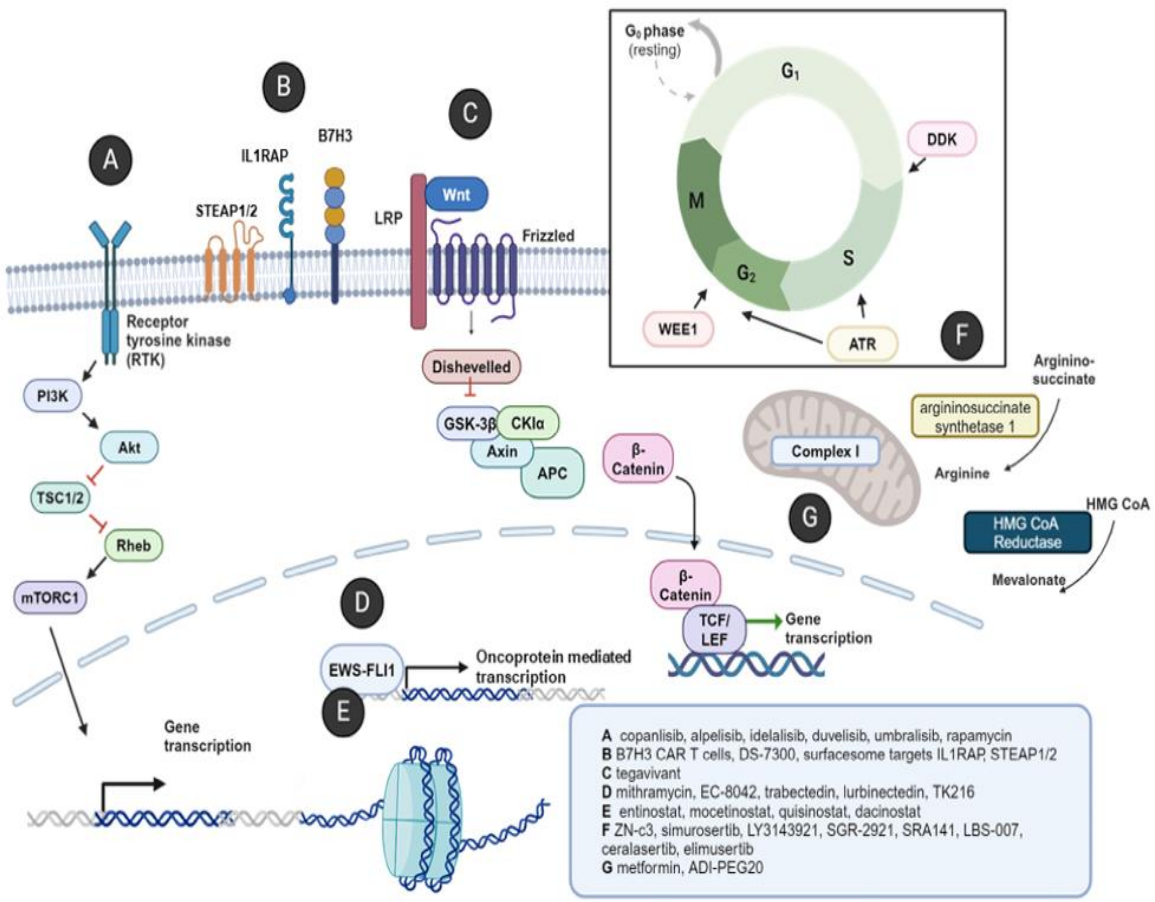
AGENTS TARGETING TUMOR METABOLISM

- Metformin + chemotherapy for targeting on glucose pathway
- Simvastatin + conventional chemotherapy for targeting on lipid metabolism

SUMMARY OF TARGETING METABOLISM

Metformin, ADI-PEG20, simvastatin [142–145, 152–156]	Glucose, lipid, amino acid metabolism	Tumor metabolism	Phase I trial completed

CONCLUSION



- Outcomes for patients with localized EWS is modest with a little improvement.
- Outcomes for patients with relapsed/refractory EWS is poor.
- For studying novel therapies, first and second strikes should consider separately.
- The heterogeneity of EWS tumor is not simple.
- There should be collaborative clinical trials for testing new agents.

NOVEL AGENTS

- **Oncoprotein target**

- Trabectedin
- Lubrinectedin
- Mithramycin

- **Epigenetic inhibition**

- Entinostat
- Mocetinostat
- Quisinostat
- Dacinostat

- **PD-1 targeting**

- Pembrolizumab

- **Cytotoxic chemotherapy**

- Doxil (liposomal doxorubicin)
- Infinatamab deruxtecan (monoclonal Ab)
- Liposomal irinotecan

- **WNT pathway**

- Tegavivint

- **Receptor tyrosine kinase inhibitor**

- Regorafenib
- Cabozanitib

- **Tumor metabolism target**

- Metformin
- Simvastatin


Thank
You!