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Novel Therapeutics

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Why do we need new treatments for prostate cancer? Don't we have enough?

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- Patients at first diagnosis of metastatic prostate cancer should be treated with testosterone lowering drugs (ADT) plus potent blockers of male hormone (androgen) signaling in cancer cells
- Chemotherapies Taxotere (docetaxel) and Jevtana (cabazitaxel) and radiopharmaceutical Pluvicto (^{177}Lu-PSMA-617) can be effective in shrinking cancer that has become resistant to hormonal drugs, but not in everyone and usually work temporarily
- The prostate cancer vaccine Provenge (sipuleucel-T) and bone-targeted radiation drug Xofigo (Radium-223) prolong survival but do not usually shrink cancer
- Recently approved treatments for prostate cancer Lynparza/Talzenna (olaparib/talazoparib) and Keytruda (pembrolizumab) are only approved for use in a minority of prostate cancer patients (<20% for Lyparza, 2-3% for Keytruda)

➢ After hormonal therapies stop working, there are limited options outside of chemo and Pluvicto that can shrink prostate cancer

Categories of new prostate cancer treatments

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- Novel ways to target the androgen receptor (AR)
  - AR degraders
- Molecularly targeted therapies
  - Drugs that block growth / survival signals in cancer cells
  - Drugs that block DNA damage repair
- Immune therapies
  - Immune checkpoint inhibitors
  - Vaccines
  - CAR-T cells
  - Bi-specific T-cell engagers
- Antibody-drug conjugates
- Radiopharmaceuticals

Why is prostate cancer treated with hormonal therapies?

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Testosterone and other male hormones stimulate prostate cancer growth and survival

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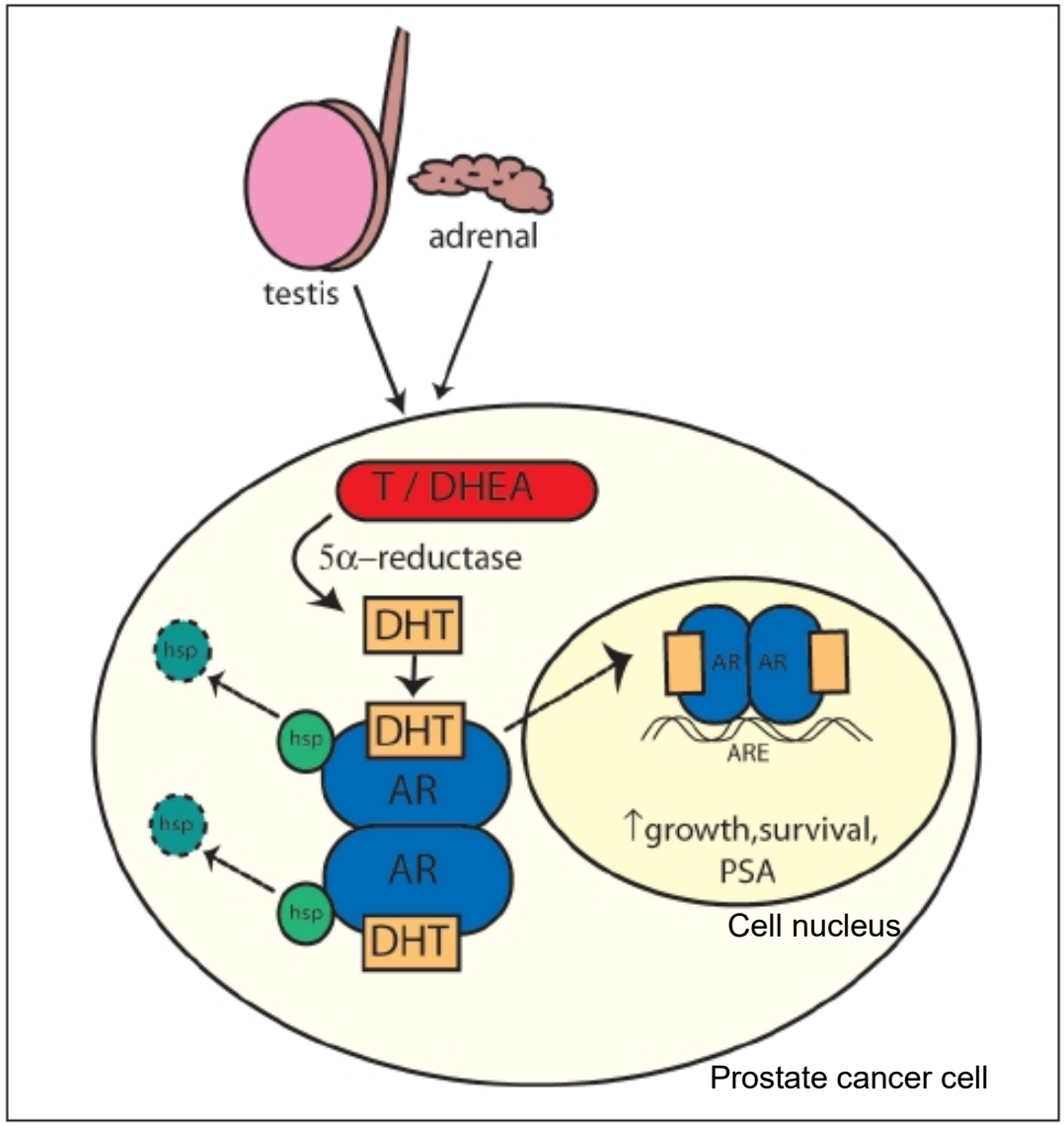

- **Testosterone** (T) produced by the testes is converted to **dihydrotestosterone** (DHT) in prostate cancer cells
- DHT binds the **Androgen Receptor** (AR), which then enters the nucleus of the cancer cell and stimulates the cell to grow and survive
- Male hormones (androgens) made by the adrenal glands (e.g. DHEA) or the prostate cancer cells themselves can also activate the androgen receptor

What is Androgen Deprivation Therapy?

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What is Androgen Deprivation Therapy?

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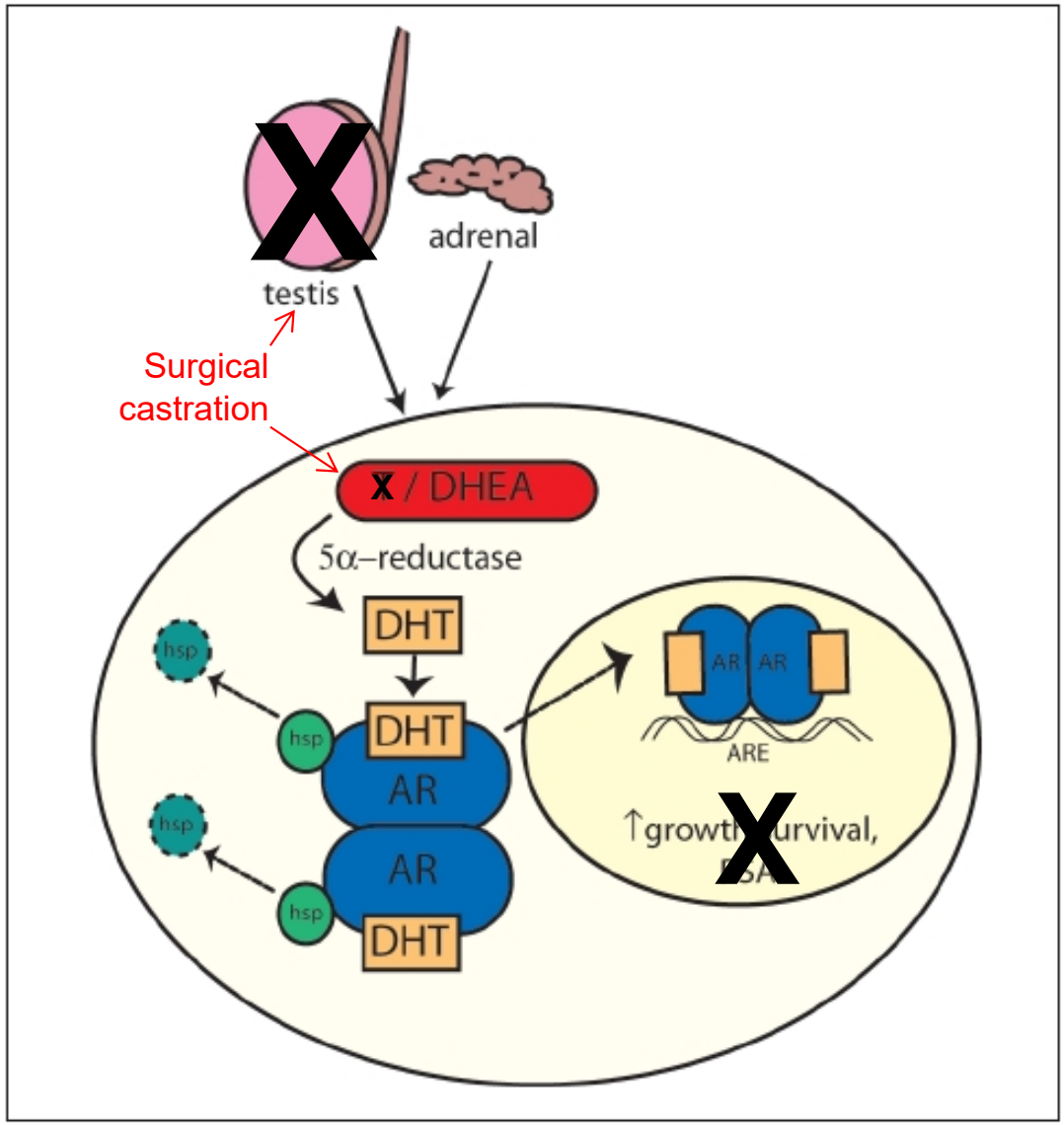

- **Androgen Deprivation Therapy (ADT)** lowers the level of testosterone in the blood, which leads prostate cancer cells to stop dividing and die
- The goal is to achieve a level of testosterone <50 ng/dL
- Can be accomplished by **surgical castration**

What is Androgen Deprivation Therapy?

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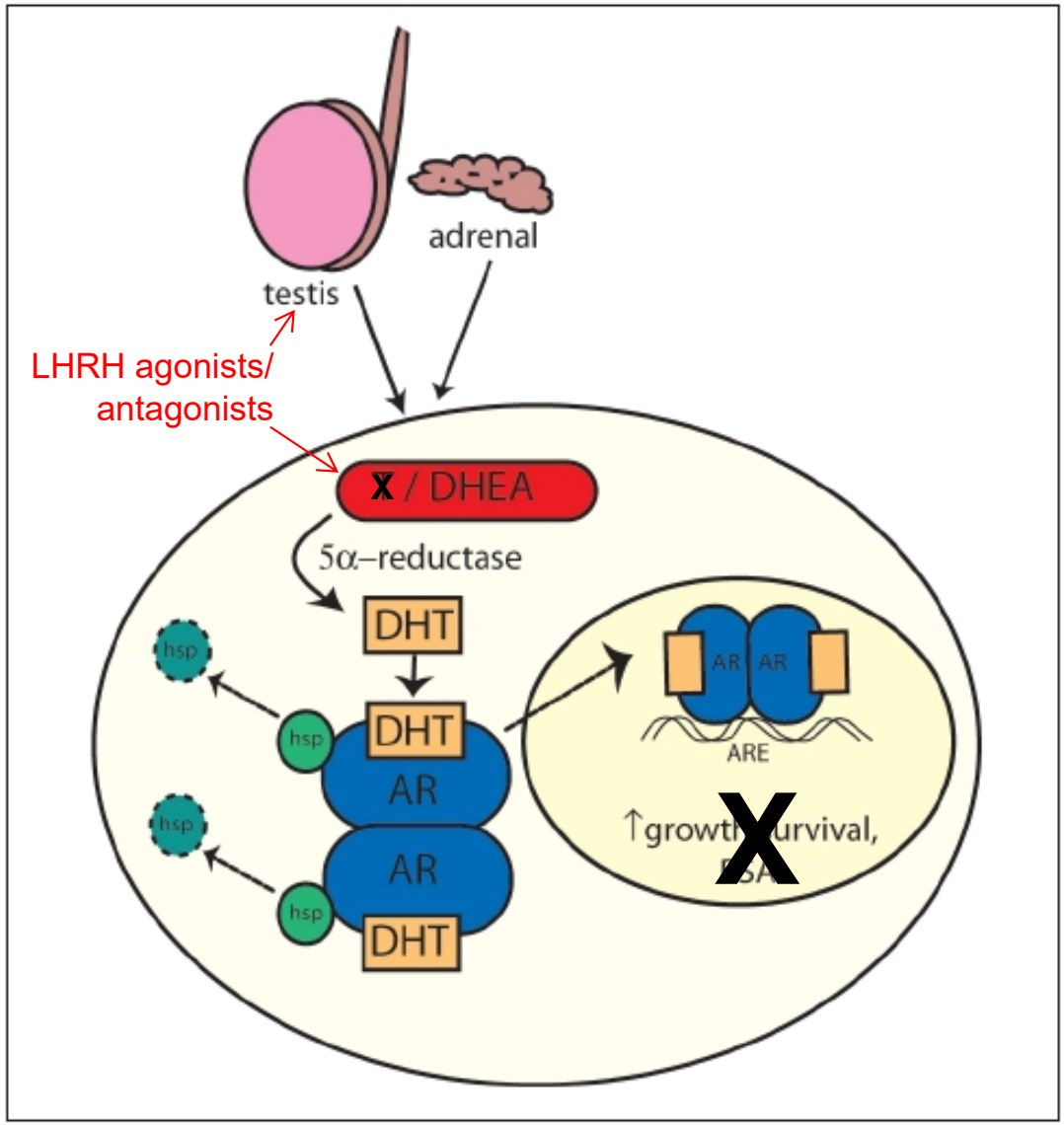

- **Androgen Deprivation Therapy (ADT)** lowers the level of testosterone in the blood, which leads prostate cancer cells to stop dividing and die
- The goal is to achieve a level of testosterone <50 ng/dL
- Can be accomplished by **surgical castration** or by injectable medications to decrease the production of testosterone by the testes, called **LHRH agonists** (e.g Lupron) or **LHRH antagonists**

What is Androgen Deprivation Therapy?

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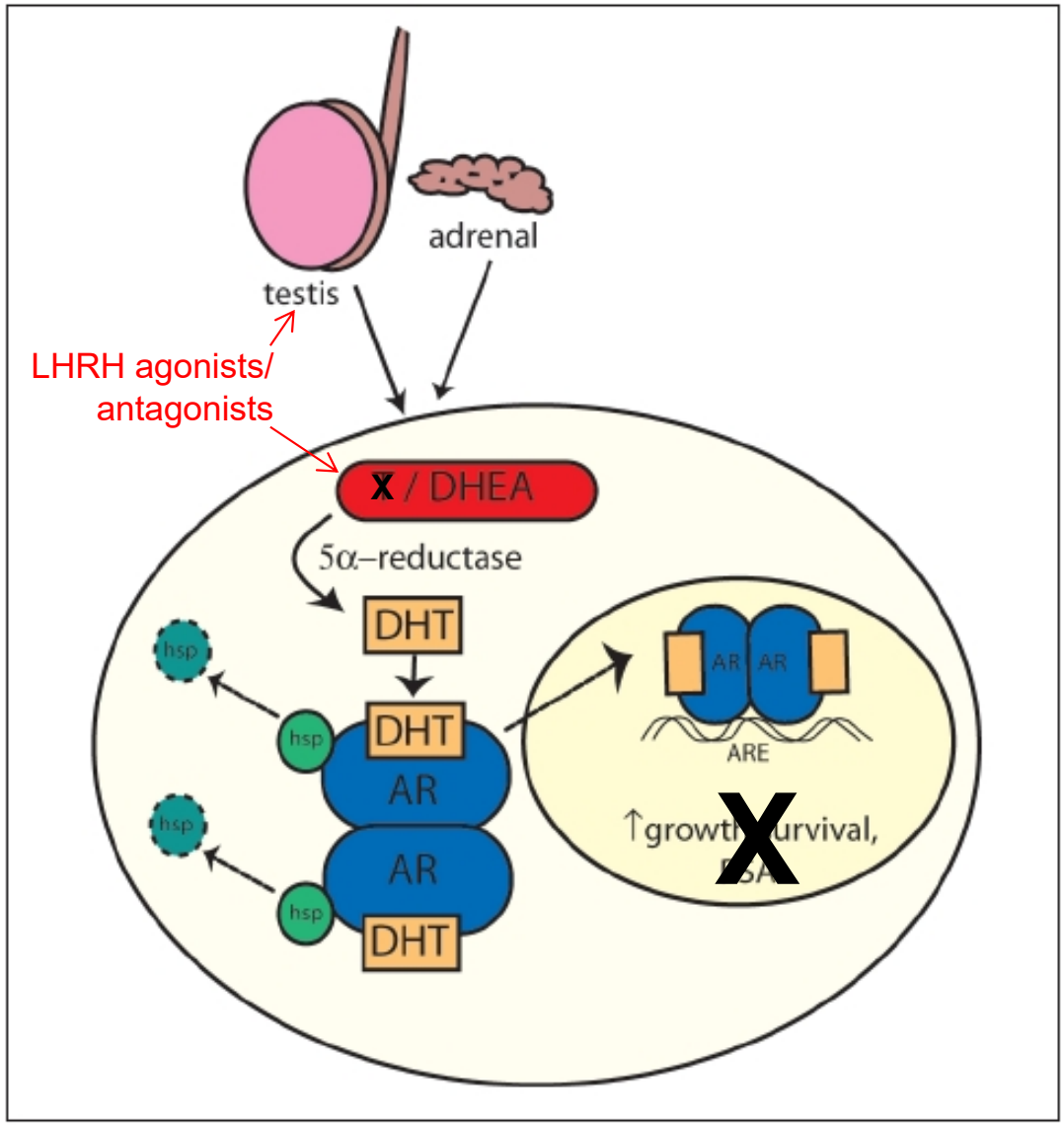

- In **metastatic disease**, ADT leads all tumors in the body (in the prostate, lymph nodes, bone, other organs) to shrink
- In **non-metastatic systemic disease** (when PSA is elevated in the blood after local treatment but tumors are not seen on scans), ADT prevents microscopic prostate cancer cells from developing into tumors
- When **combined with radiation**, ADT can prevent cancer cells from surviving damage caused by the radiation, and kill microscopic cells located elsewhere in the body

What other hormonal drugs are used in prostate cancer?

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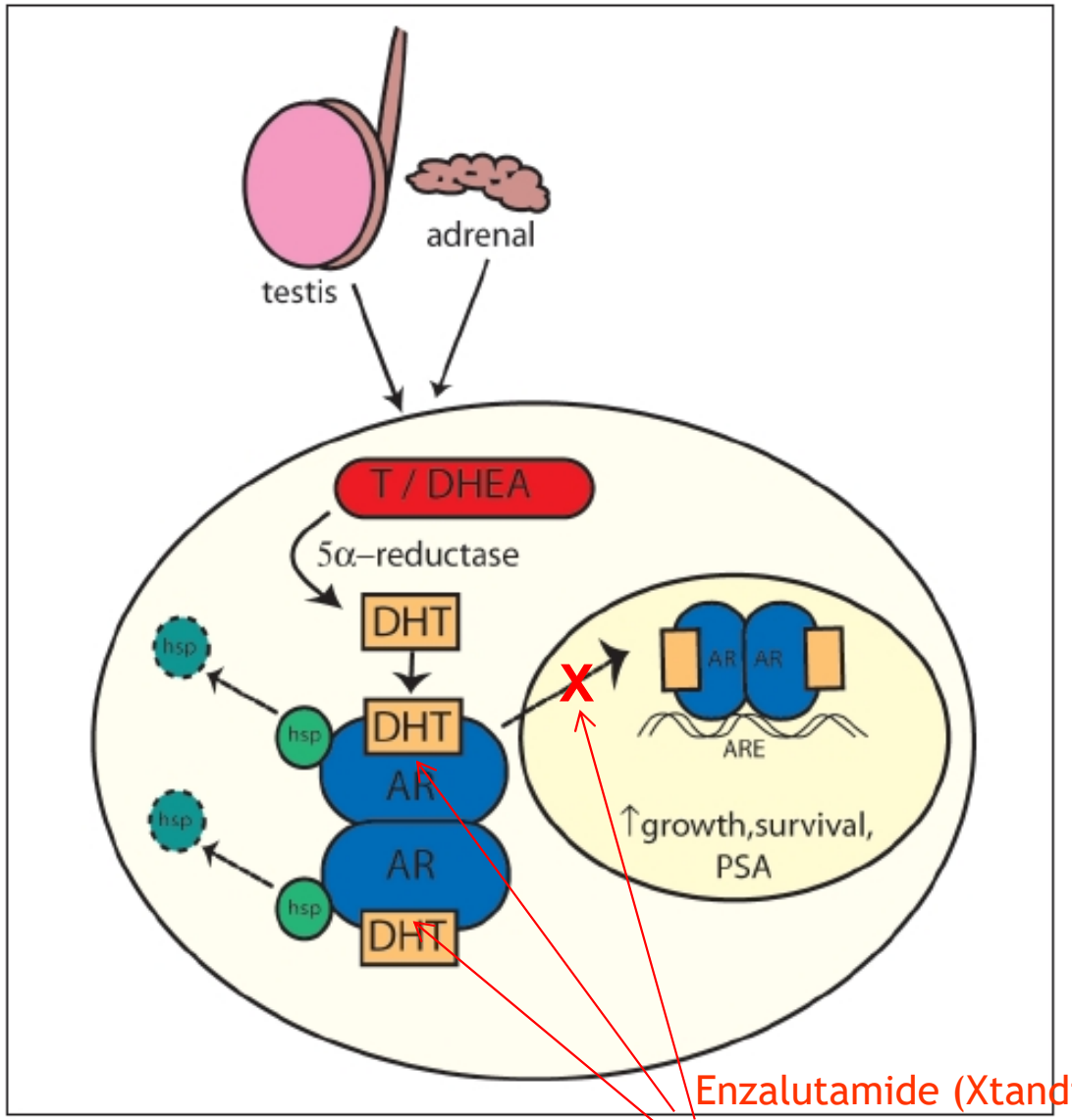

Potent novel anti-androgens

- Block binding of DHT (and other male hormones) to the AR
- Prevent the AR from entering the nucleus
- Combined with ADT at initial diagnosis of metastatic prostate cancer, or used when ADT stops working

What other hormonal drugs are used in prostate cancer?

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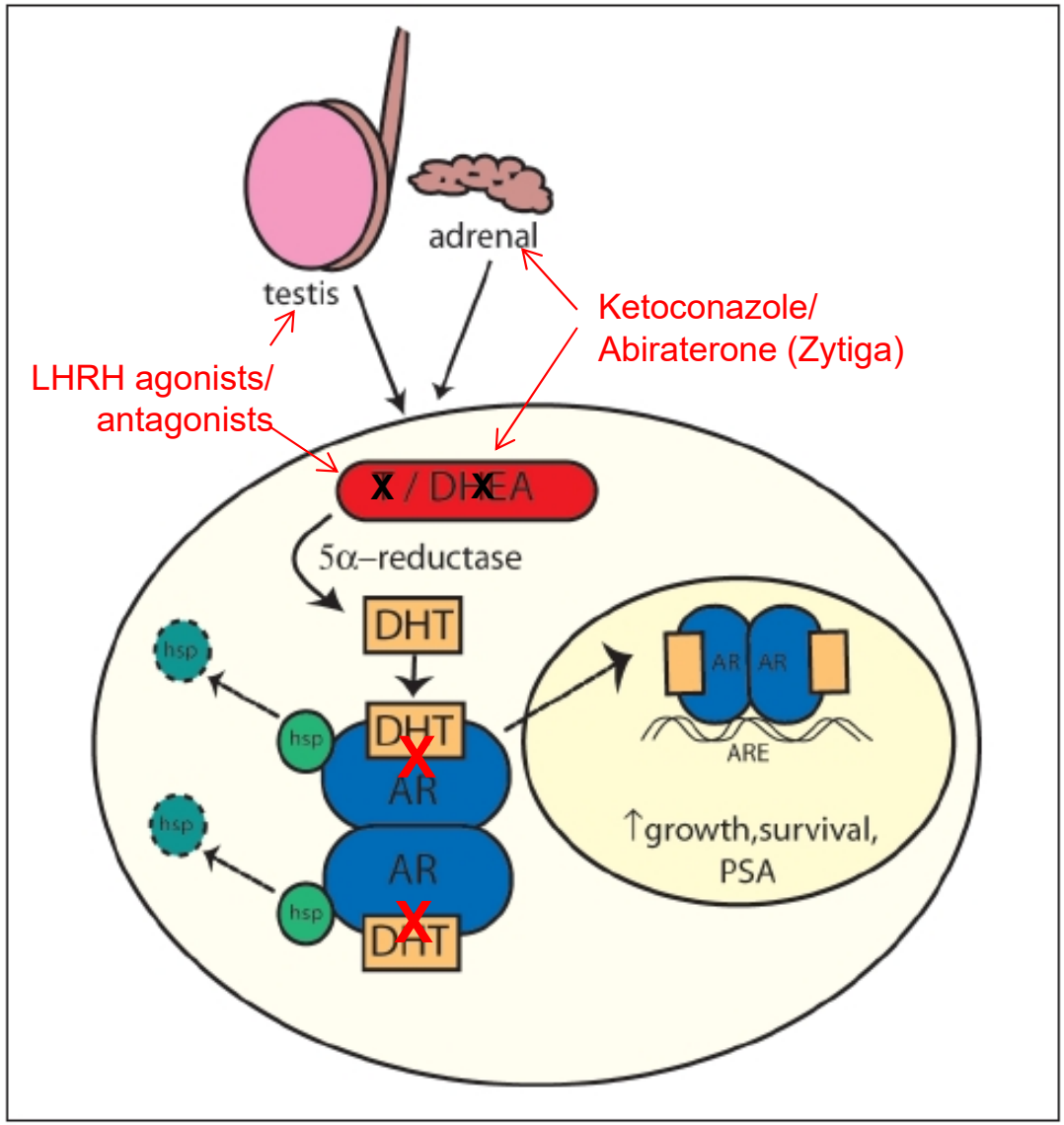

Adrenal inhibitors

- Ketoconazole and **abiraterone (Zytiga)** used when ADT stops working

It's 2025 - shouldn't we be using genetically/molecularly targeted therapies?

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- Signaling through the Androgen Receptor is the most important molecular pathway driving prostate cancer cell growth and survival
  - Androgen deprivation therapy is **molecularly targeted therapy**
- When ADT stops working (the cancer is "castration-resistant"), this is frequently due to alterations in the gene encoding the Androgen Receptor
  - Novel drugs that target Androgen Receptor signaling (abiraterone, enzalutamide) in castration resistant prostate cancer are **genetically targeted** agents

What are changes in AR signaling that lead to "castration resistance"?

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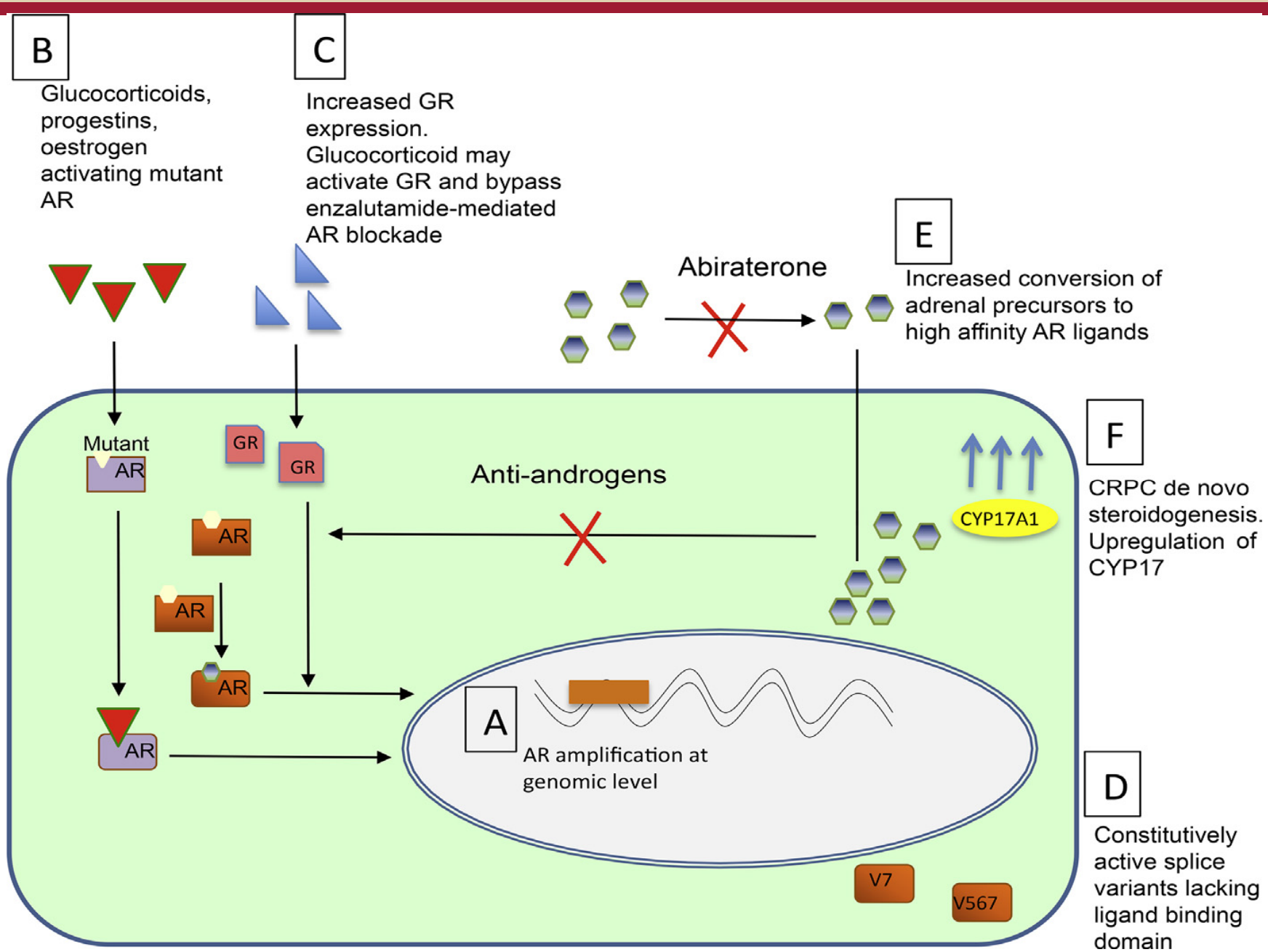

Categories of new prostate cancer treatments

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- Novel ways to target the androgen receptor (AR)
  - AR degraders – luxdegalutamide (ARV-766, JSB462), BMS-986365 (CC-94676)
- Molecularly targeted therapies
  - Drugs that block growth / survival signals in cancer cells
  - Drugs that block DNA damage repair
- Immune therapies
  - Immune checkpoint inhibitors
  - Vaccines
  - Bi-specific T-cell engagers
  - CAR-T cells
- Antibody-drug conjugates
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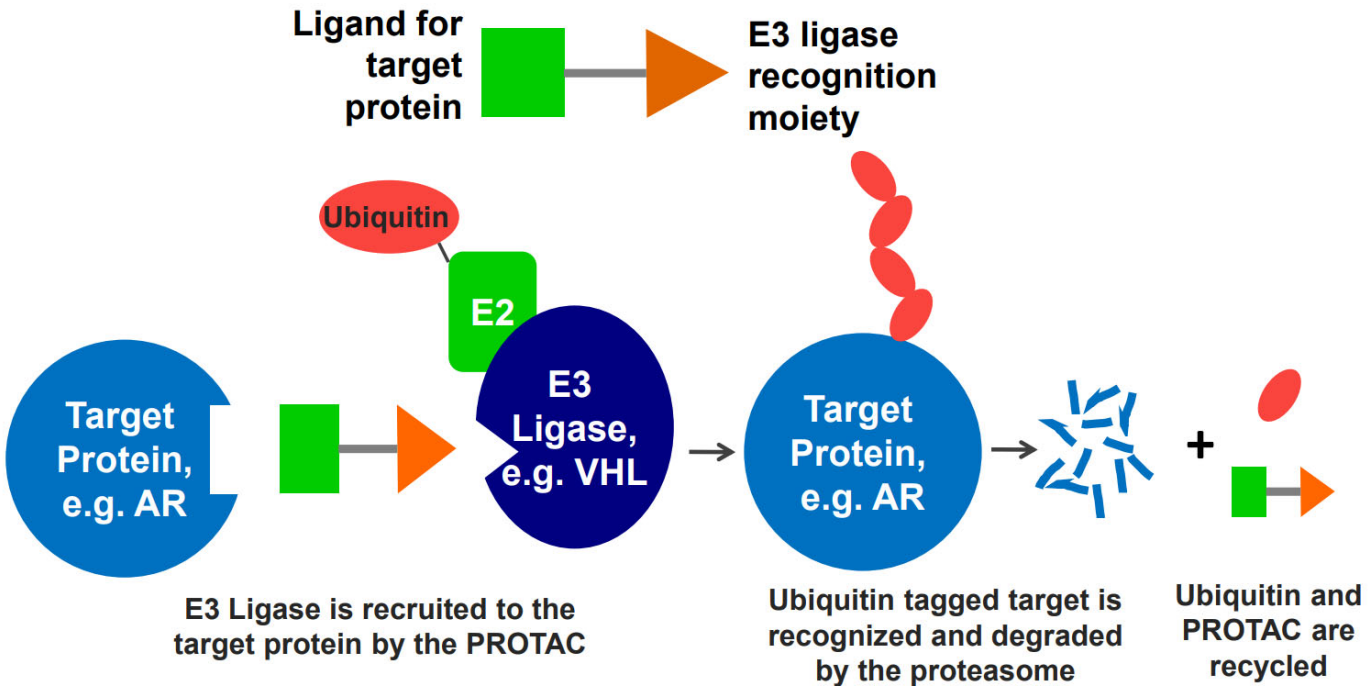
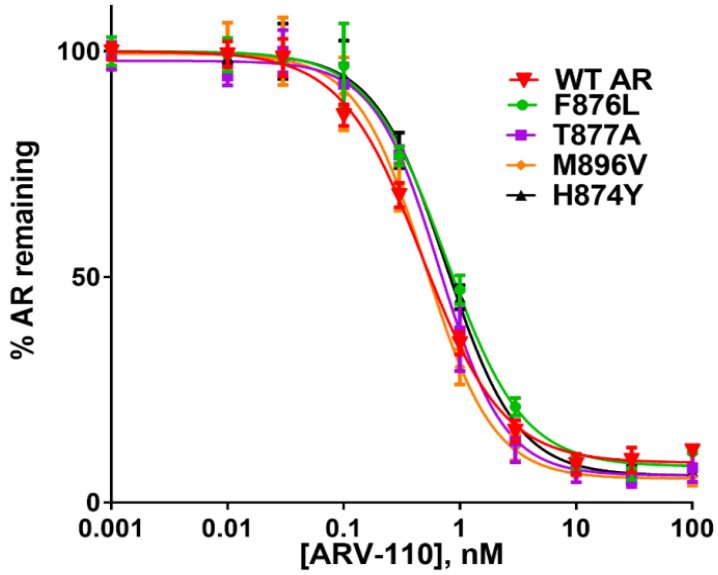
PROTAC: PROteolysis TArgeting Chimera

- Technology developed by Prof. Craig Crews, Yale University
- Arvinas founded in 2013



- AR point mutations are amenable to ARV-110 mediated degradation



Neklesa T, et al. DOI: 10.1200/JCO.2019.37.7_suppl.259
Journal of Clinical Oncology 37, no. 7_suppl (March 1 2019) 259-259.

Categories of new prostate cancer treatments

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- Novel ways to target the androgen receptor (AR)
  - AR degraders
- Molecularly targeted therapies
  - Drugs that block growth / survival signals – capivasertib (AKT), cabozantinib (MET,VEGFR2), mevrometostat (EZH2)
  - Drugs that block DNA damage repair
- Immune therapies
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Mechanism of action of capivasertib

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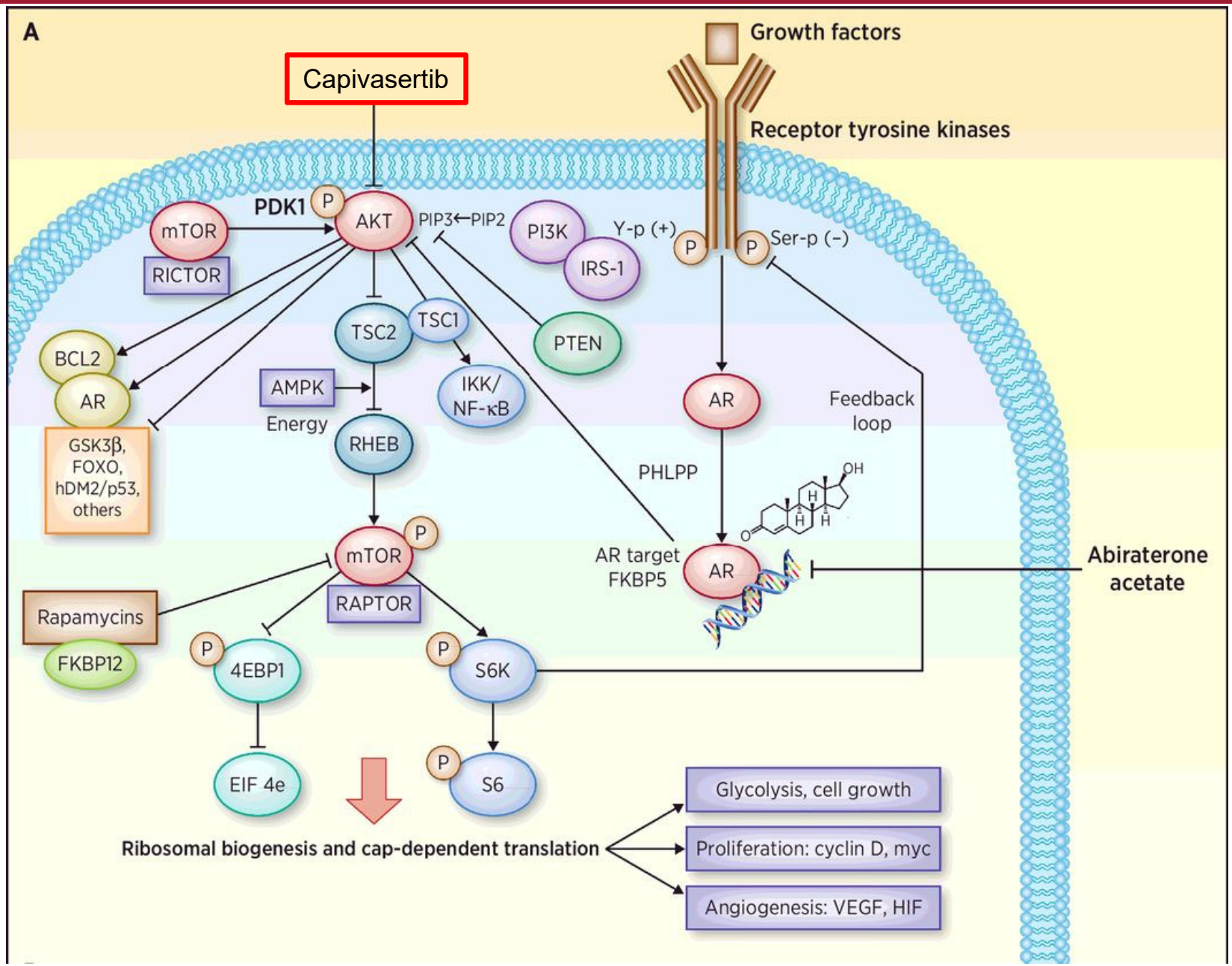

Mechanism of action of cabozantinib

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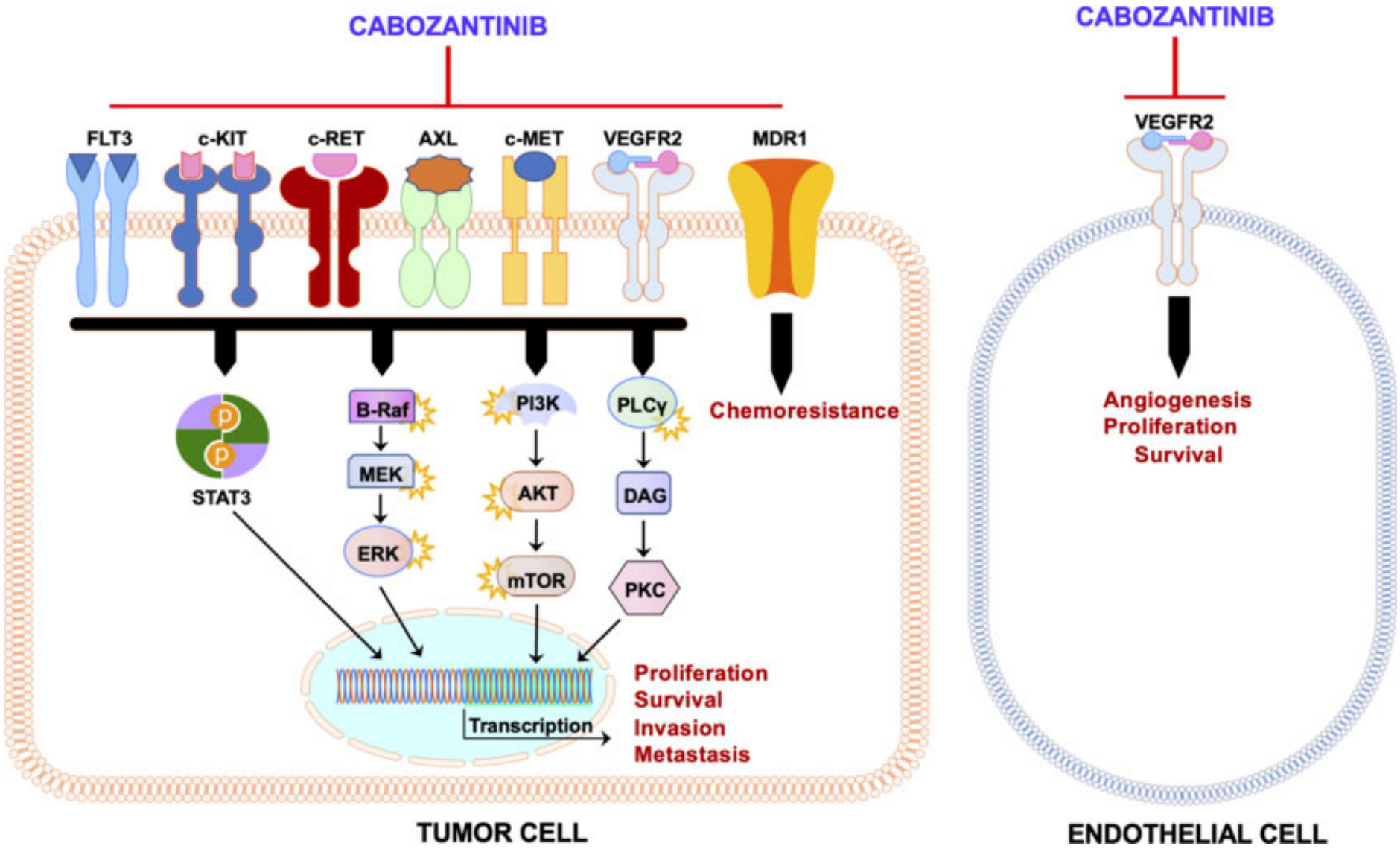

Mechanism of action of mevrometostat

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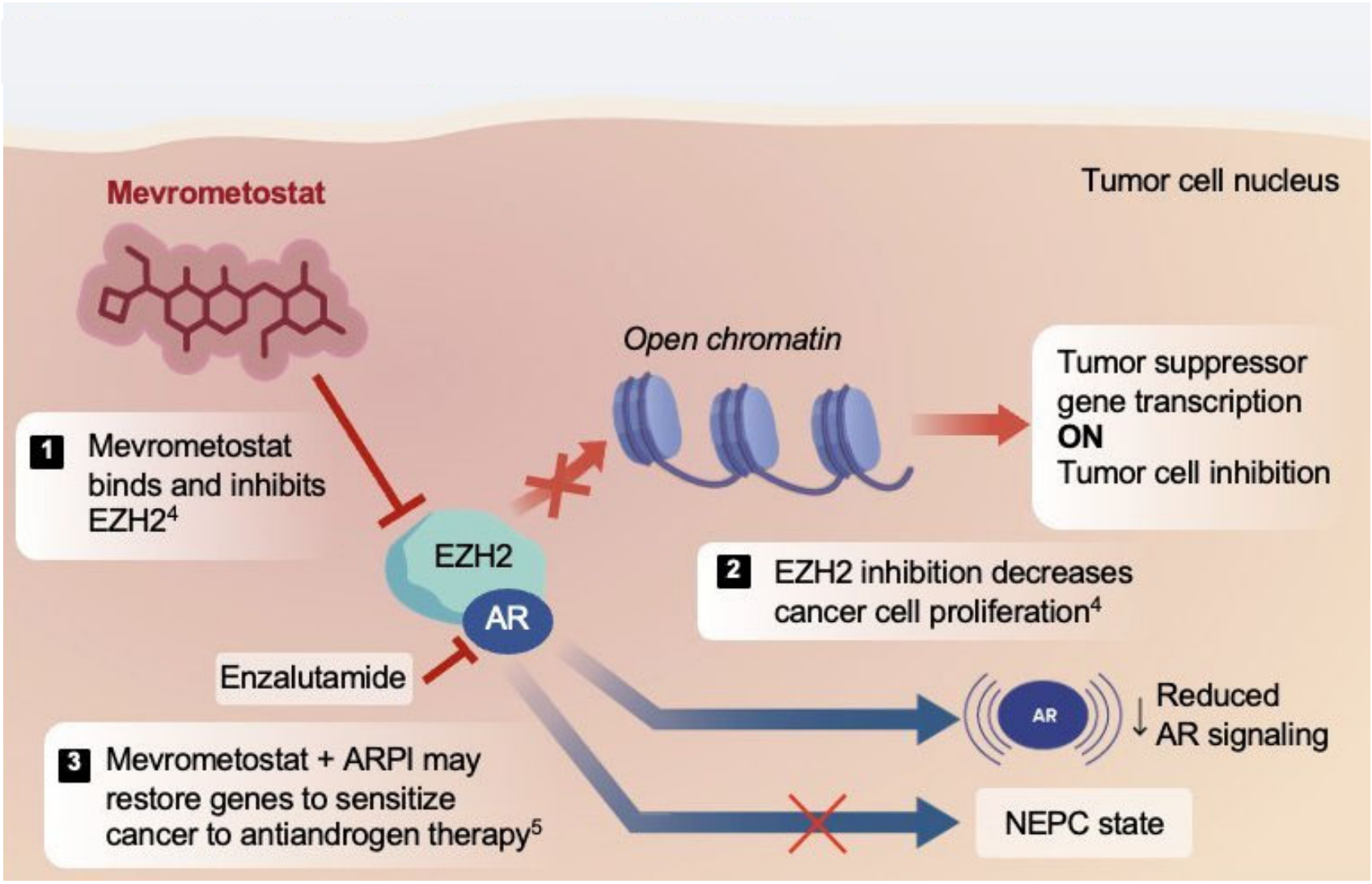

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- Novel ways to target the androgen receptor (AR)
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  - Drugs that block DNA damage repair – PARP inhibitors
- Immune therapies
  - Immune checkpoint inhibitors
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Mechanism of action of PARP inhibitors (olaparib, talazoparib, rucaparib, niraparib)

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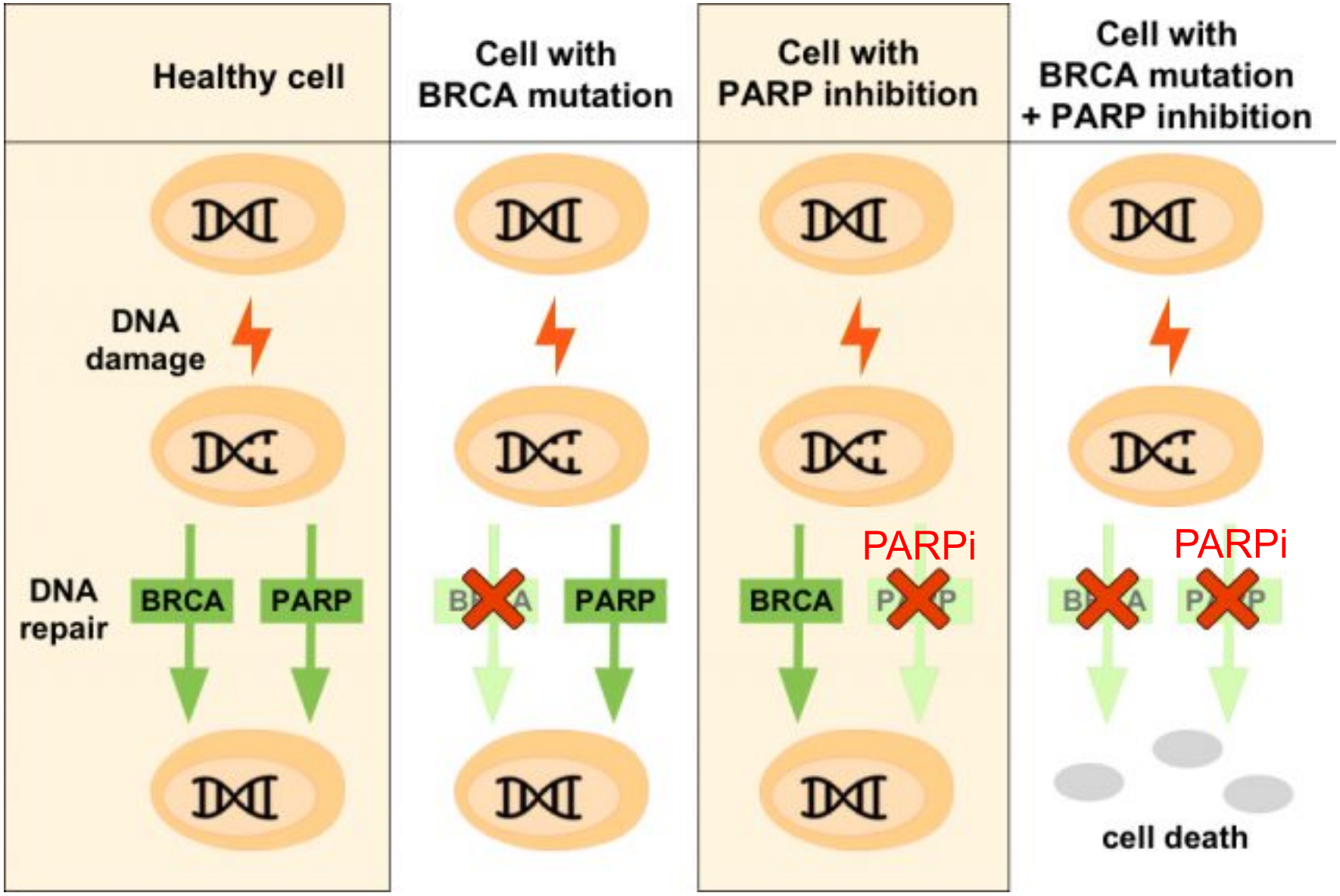

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- Immune therapies
  - Immune checkpoint inhibitors – pembrolizumab (PD-1), atezolizumab (PD-L1)
  - Vaccines – sipuleucel-T (Provenge)
  - CAR-T cells
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Immunotherapy approaches in cancer

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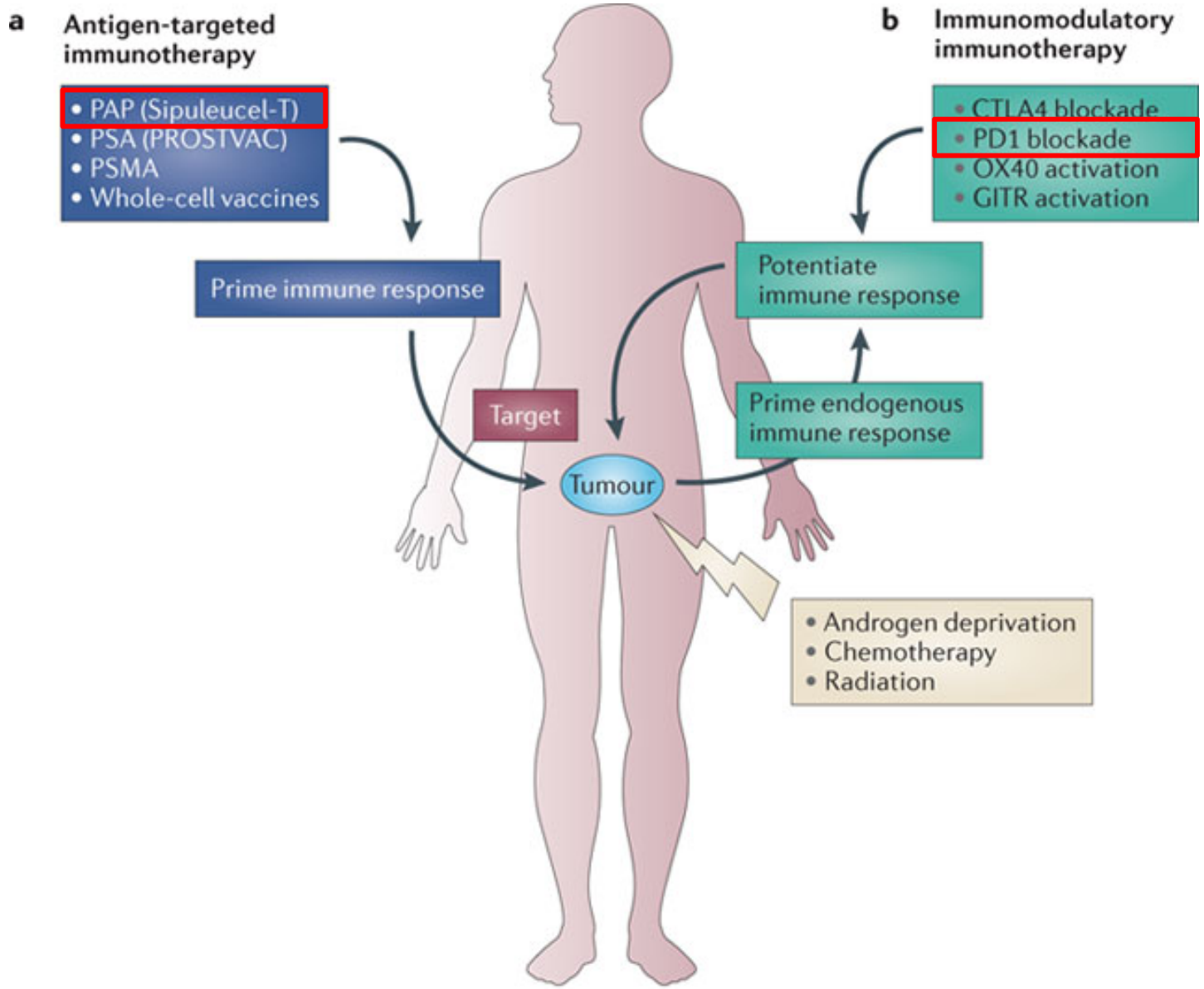

- pembrolizumab (Keytruda)
- PD-L1 blockade: atezolizumab (Tecentriq)

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CAR-T cells

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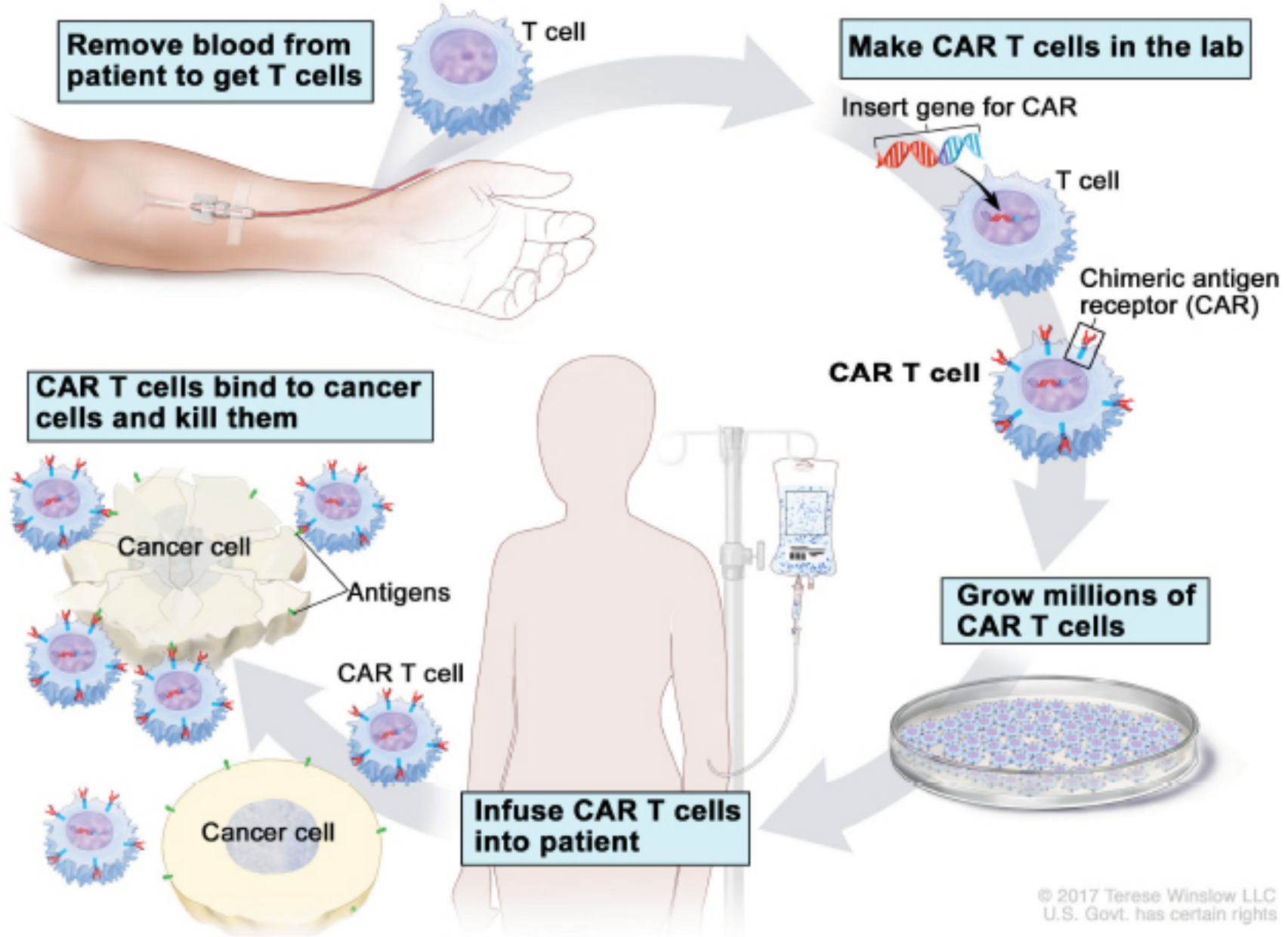

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Mechanism of action of Bi-specific T-cell Engager (BiTEs)

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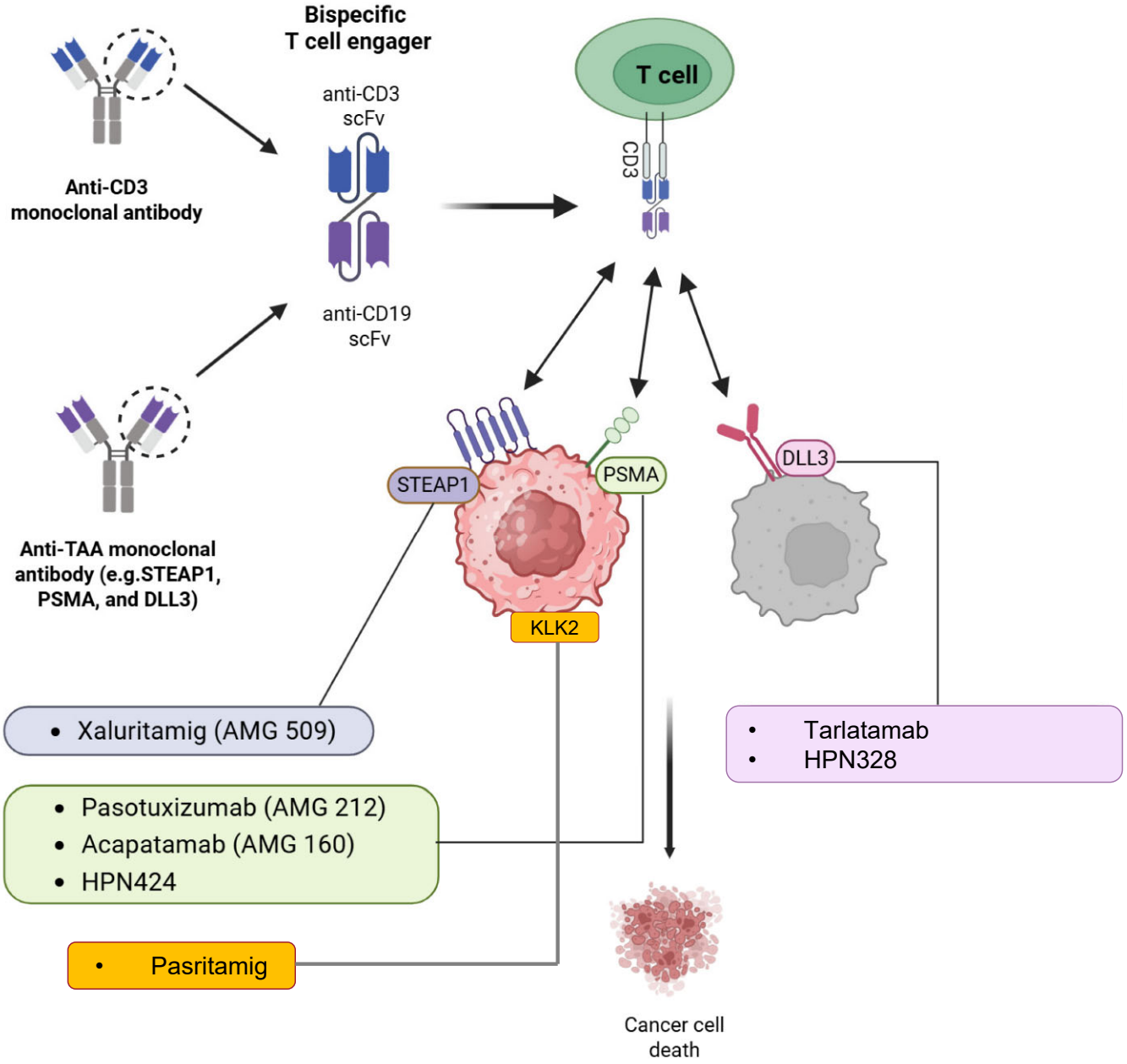

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Antibody-drug conjugates in prostate cancer

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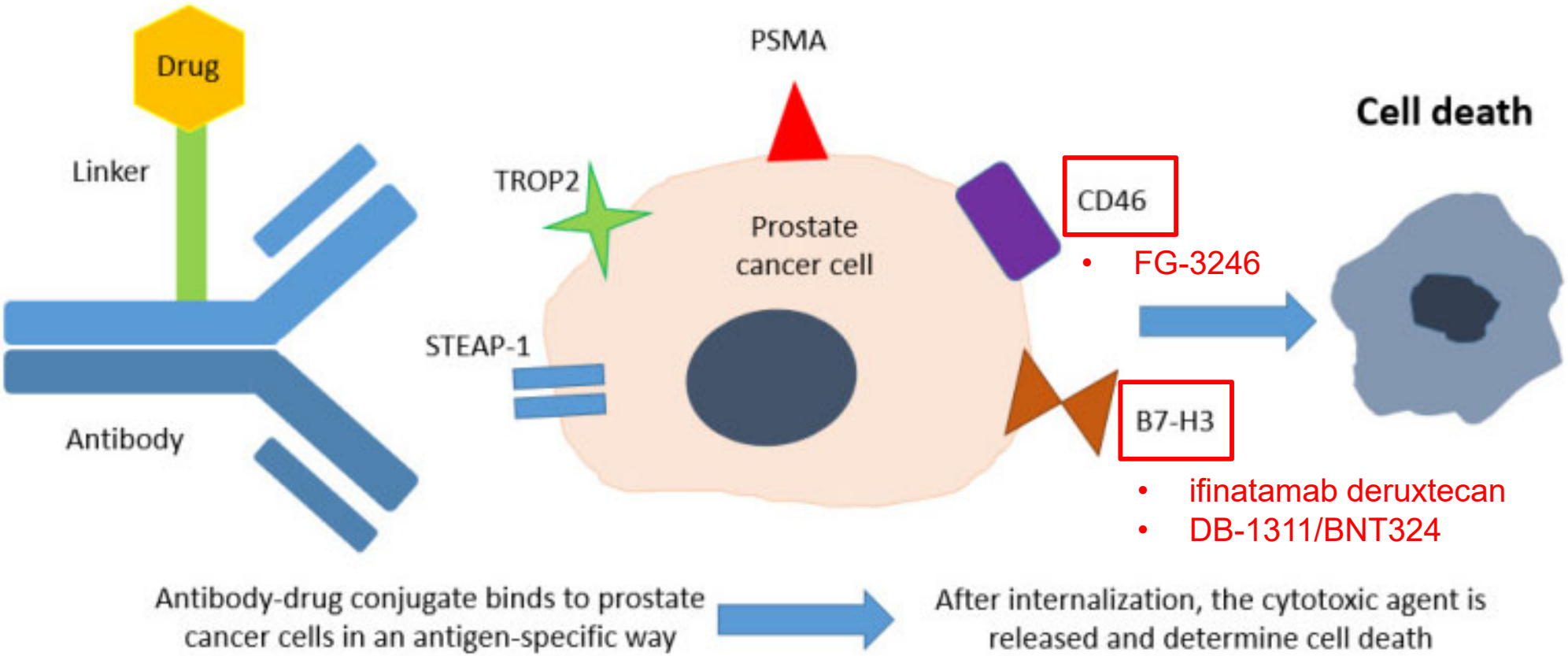

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Radiopharmaceuticals

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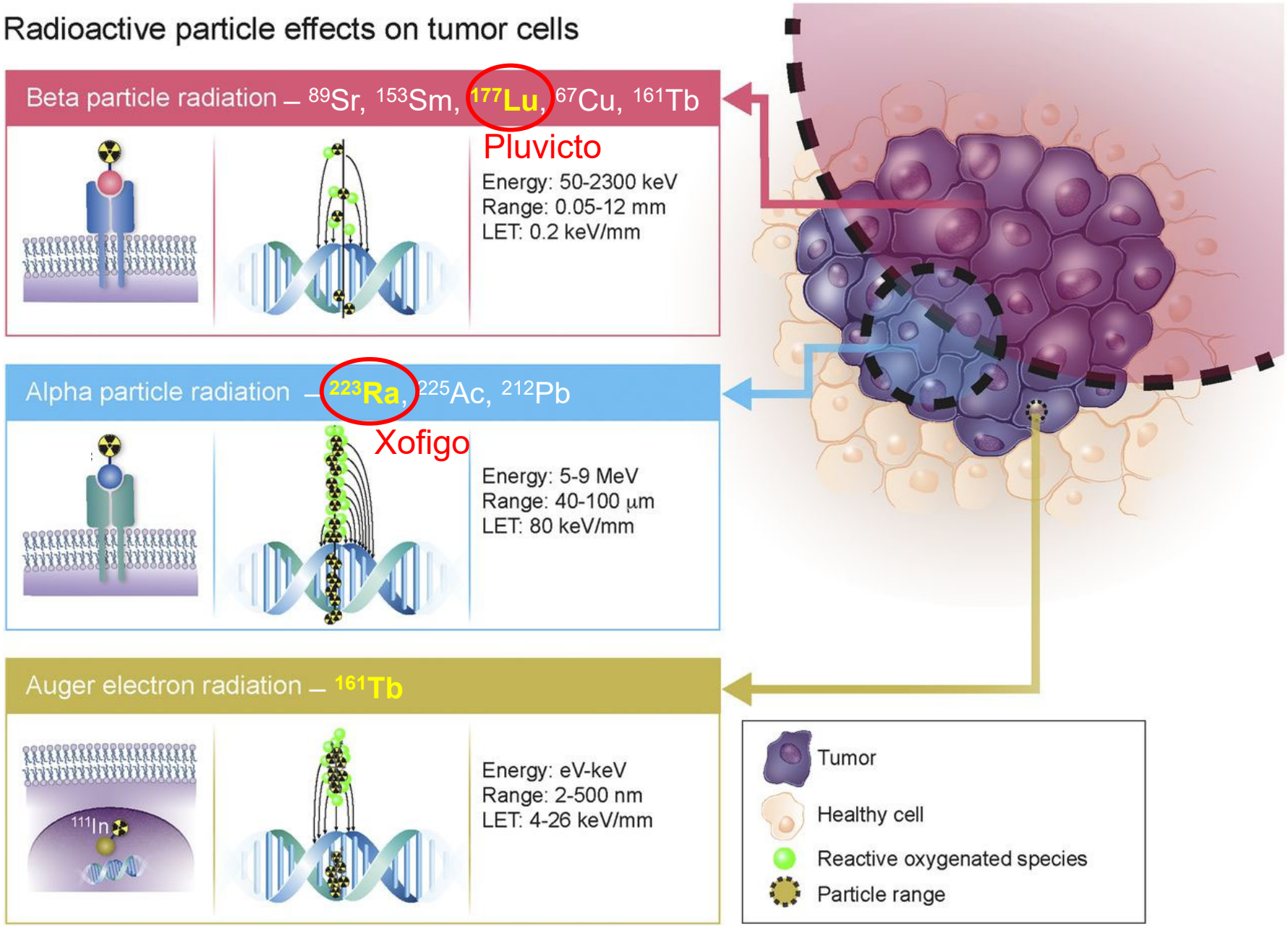

Mechanism of action of Radium-223

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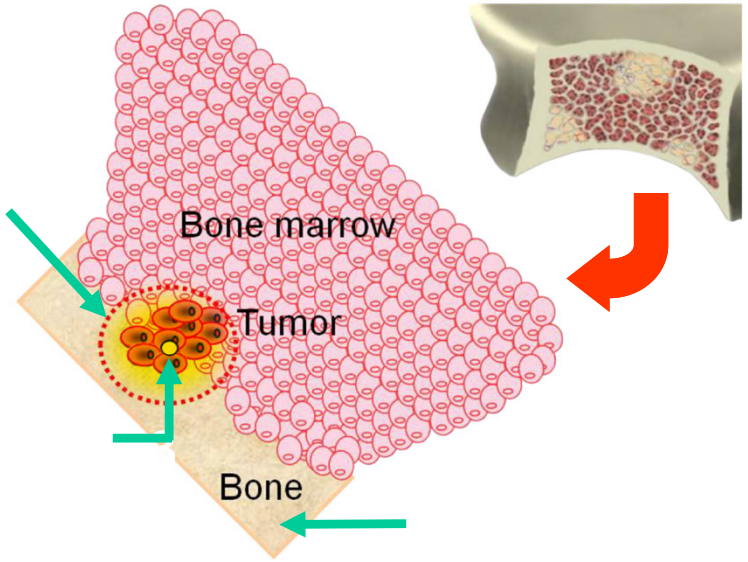

- Radium-223 acts as a calcium mimic
- Naturally targets new bone growth in and around bone metastases
- Alpha-particles induce double-strand DNA breaks in adjacent tumour cells
- Short penetration of alpha emitters (2-10 cell diameters) = highly localized tumour cell killing and minimal damage to surrounding normal tissue

^{177}Lu-PSMA-617 targeted radioligand therapy

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