Lecture Outline

1. Jan 15 - The Problem, The Prostate, and The Man
2. Jan 22 - What is Cancer?
3. Jan 29 - The Causes of Prostate Cancer
4. Feb 5 - Diagnosing Prostate Cancer
5. Feb 12 - Treating Prostate Cancer
6. Feb 19 - Prostate Cancer Metastasis
7. TODAY - Hormones and Prostate Cancer
8. March 5 - Emerging and Novel Treatment Techniques - Hope for the Future

If You Recall…Lecture 6
Prostate Cancer Metastasis

- Metastasis is the process where tumor cells travel to other organs and form secondary tumors within that organ.
- Metastasis is organ-specific. Anatomical vs. Environmental Debate.
- Bone turnover is mediated by osteoblasts and osteoclasts.
- Prostate cancer metastases are primarily osteoblastic (bone forming).
- Prostate cancer cell dissemination is early and widespread, but cancer cell growth is inefficient.

Hormones and Prostate Cancer

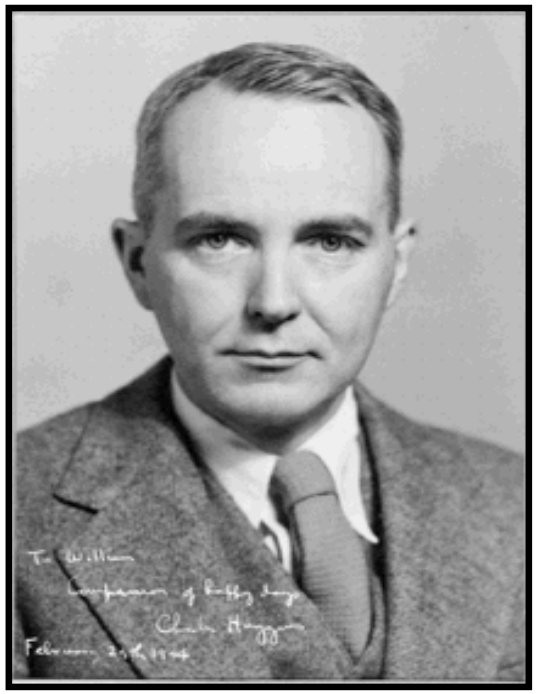
- History of Androgens and Prostate Growth Control and the Work of Charles Huggins
- Androgen Production and Regulation
- The Androgen Receptor
- Blocking Androgens
- Hormone-Refractory Prostate Cancer (HRPC)

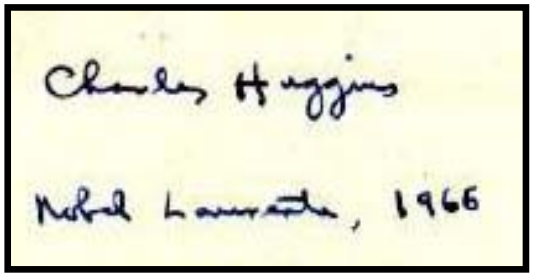
History of Androgen Therapy

- 1786: John Hunter described seasonal variations in the size of the testicles and prostate gland in animals. Later tested the effects of castration on secondary sex organs.
- 1893: William White measured changes in the prostate gland after castration using dogs. Proposed using castration to treat urinary obstruction disorders.
- 1935: Clyde Deming reported that castration decreased the size of the prostate in primates but had no effect on BPH.
- Late 1930s: Gutman and Gutman reported that serum Acid-Phosphatase levels increased in patients with metastatic prostate cancer.

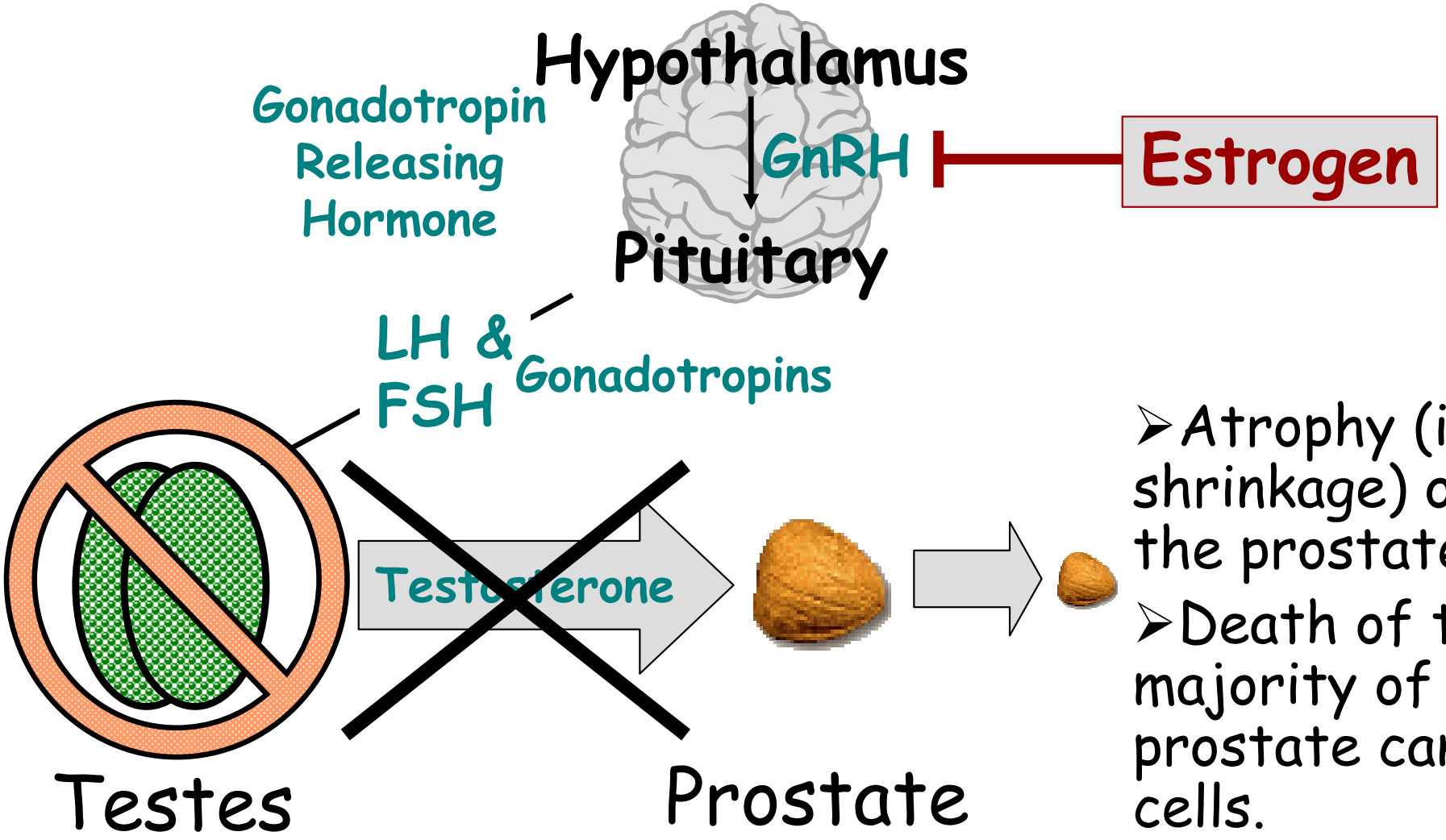
History of Androgen Therapy: Charles B. Huggins

- In 1940 Huggins reported that testosterone removal (castration) resulted in rapid shrinkage of the enlarged prostate of older dogs.
- In 1941 Huggins and Hodges reported that androgen removal greatly aided patients with advanced prostate cancer.
- "Prostatic cancer is influenced by androgenic activity in the body."
- Later that year, Huggins reported that oral estrogens had the same effect as castration for prostate cancer patients.





Androgen Ablation Kills Prostate Cells



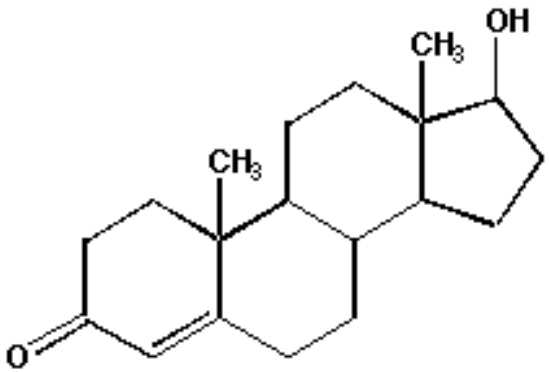
- Atrophy (i.e. shrinkage) of the prostate
- Death of the majority of prostate cancer cells.

After Charles Huggins' Discovery

- 1960's: Large studies testing oral estrogens and castration for prostate cancer treatment. Found that oral estrogens caused significant cardiovascular complications.
- 1960's-1980's: New approaches were developed to either block androgen production or interfere with androgen activity.
- Today: Hormone therapy (androgen ablation) is still common practice for advanced prostate cancers. A variety of agents are available to block androgens.

Hormones and the Prostate

- The growth and development of the prostate gland is dependent upon the presence of androgens (male hormones).
- The most common androgen is testosterone, a steroid hormone.
- Testosterone is produced in the testes.

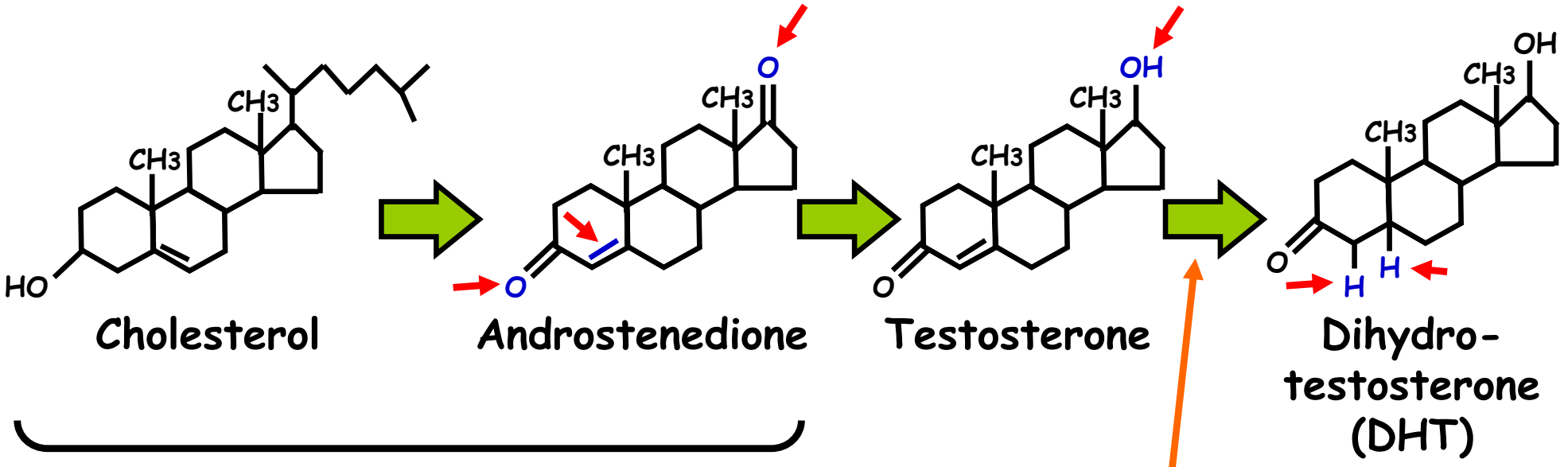


Testosterone

Production of Androgens

Testes:
Secrete Testosterone

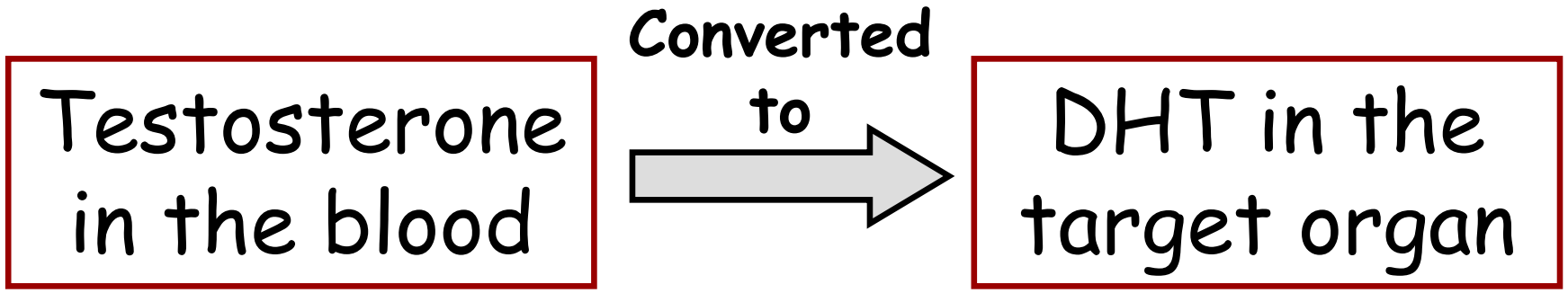
Target Organ:
Testosterone to DHT



Adrenal Glands:
Secrete Androstenedione

Converting Enzyme:
5-alpha-Reductase

Effects of Testosterone on the Body



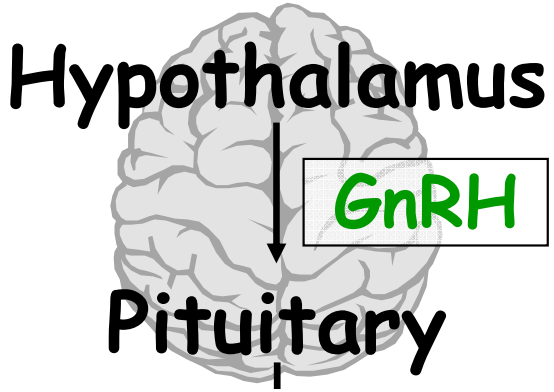
Organs

- Hair
- Muscle
- Brain
- Testes
- Sex Accessory Tissues (Prostate)

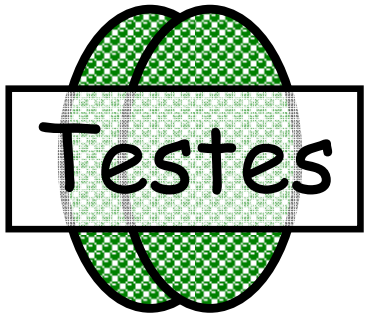
Behavior and Reproduction

- Aggression
- Libido
- Spermatogenesis
- Potency

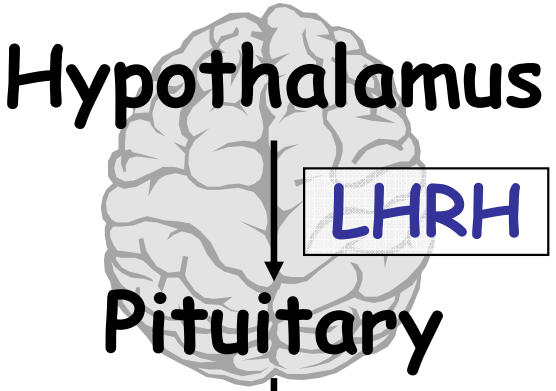
Regulation of Androgens: The Testes



LH & FSH



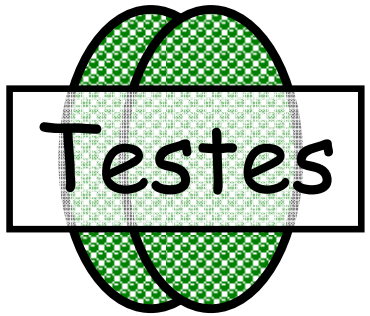
Testosterone Production (LH) and Spermatogenesis (FSH)



Leutenizing Hormone Releasing Hormone

LH

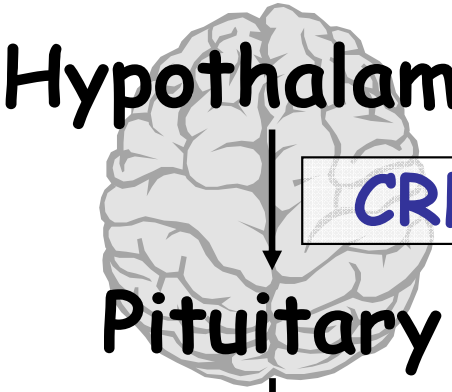
Leutenizing Hormone



Testosterone Production

Accounts for 95% of total androgens

Regulation of Androgens: The Adrenal Glands



Corticotropic Releasing Hormone

ACTH

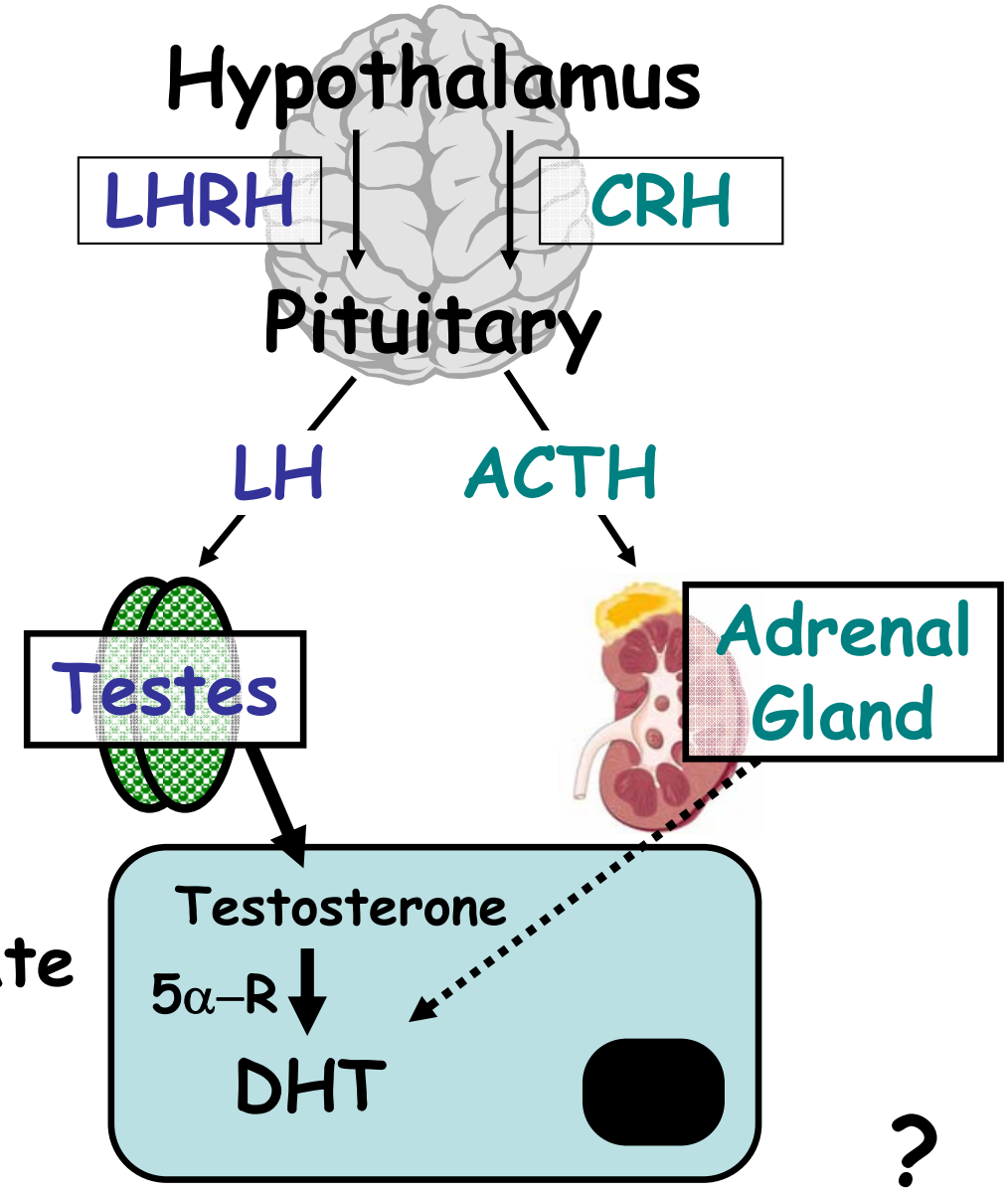
Adrenal Corticotropic Hormone

Androstenedione Production from Adrenal Gland

Accounts for 5% of total androgens

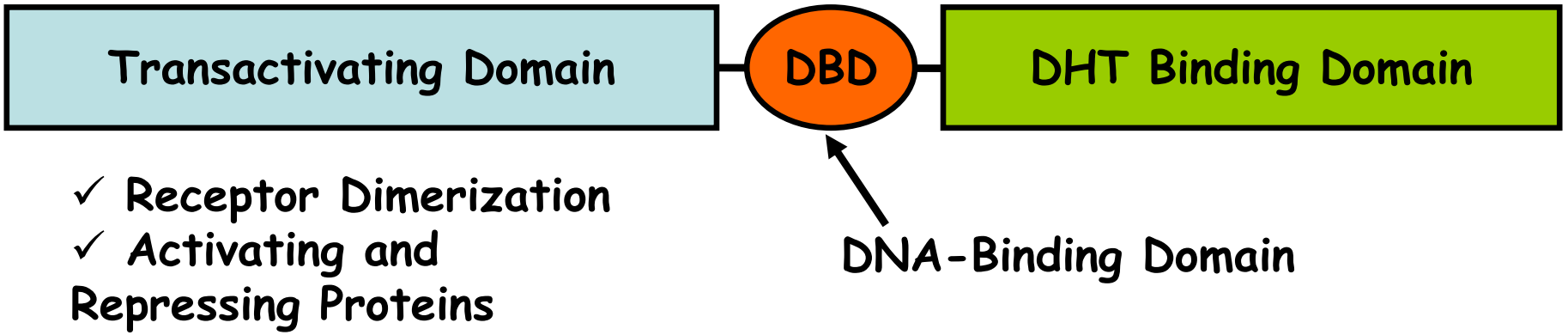
Androgen Control of Prostate Growth

- Testosterone is converted to DHT by 5a-Reductase upon entering the prostate cell.
- DHT binds to a receptor and changes gene expression.
- Androstenedione can weakly mimic the effect of DHT.

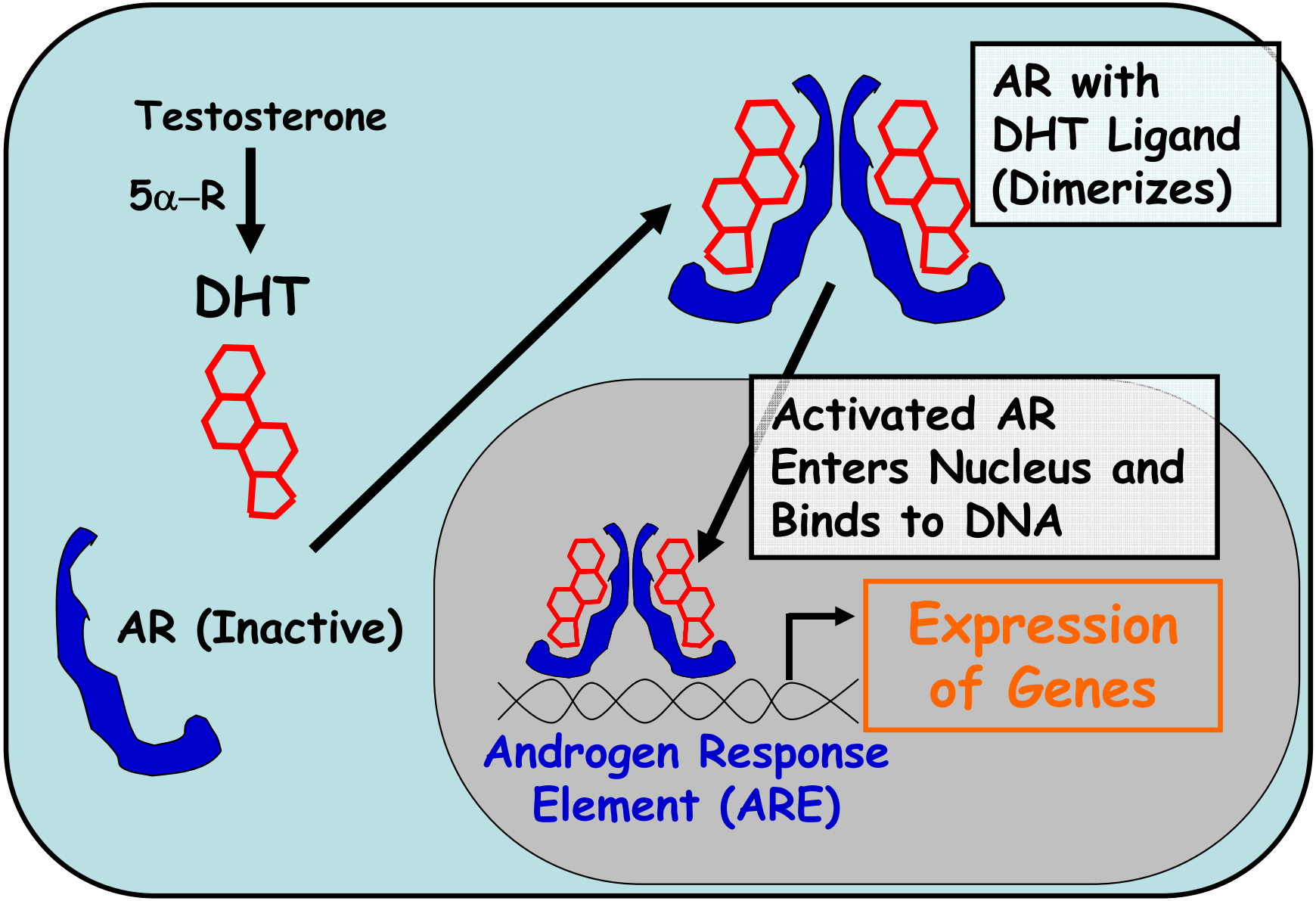


The Androgen Receptor (AR)

- Intracellular hormone receptor.
- Present in tissues that respond to androgens.
- AR protein has three domains, each with a unique function.
- The AR promotes the expression of genes that are hormonally controlled.



DHT and the AR



Prostate Cell

Androgen-Response Elements (AREs)

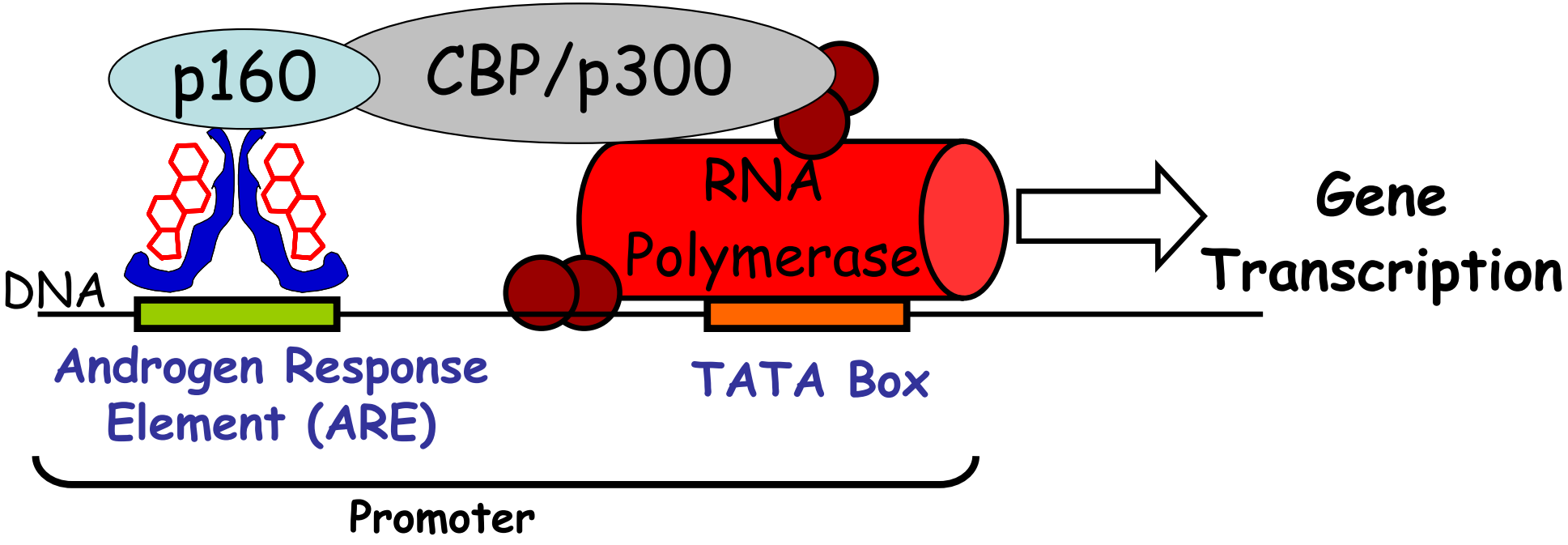
- Androgen Response Elements are specific DNA-sequences that activated ARs bind to.
- Consensus DNA sequence is TGTTCT.
- AREs are located within the promoter of a gene, the region where its protein expression is controlled.
- Activated ARs binding to AREs promote (or repress) the expression of the gene.

Promoter (controls gene expression)

Gene (encodes for a protein)

AR binding to ARE

- The Androgen Receptor (AR) complexed with DHT binds to the ARE on the DNA and promotes gene expression.
- It promotes gene expression by recruiting other proteins necessary for making a RNA message (p160, CBP/p300, RNA Polymerase, and others).
- Gene expression = DNA to RNA message to Protein

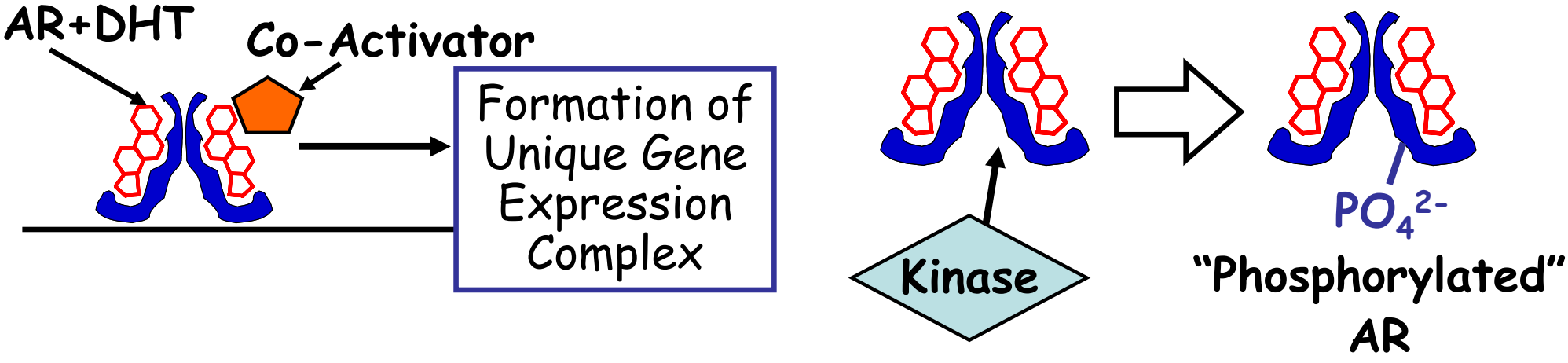


Genes with AREs

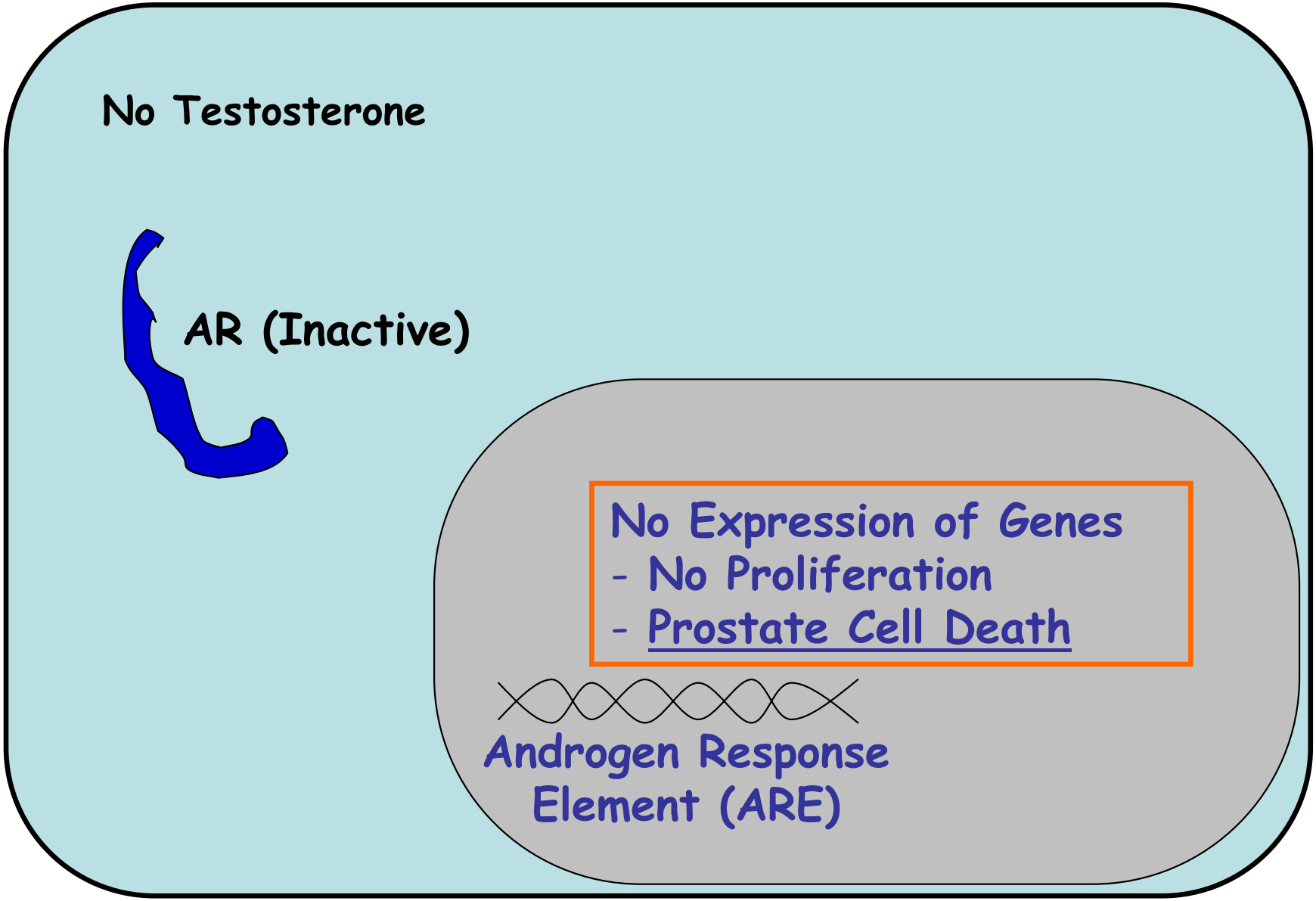
- Genes whose expression are controlled by androgens.
- Prostate:
  - **Cell Proliferation Genes**: promote cell division (ex. CDKs and Cyclins) and secrete growth factors (ex. IGF, FGF, EGF).
  - **Cell Survival Genes**: suppress apoptosis (ex.TGF-β and receptors).
  - **PSA**, hK2, and other prostate secretory products.

Factors that Modulate AR Activity

- Many proteins influence the function of the Androgen Receptor.
- Co-Activators interact with and change the gene-expression complexes. Example: *Androgen Receptor-Associated (ARA) proteins*.
- Kinases are proteins that directly change the Androgen Receptor by adding phosphates (PO_4^{2-}). Example: *Mitogen Activated Protein (MAP) Kinases*.



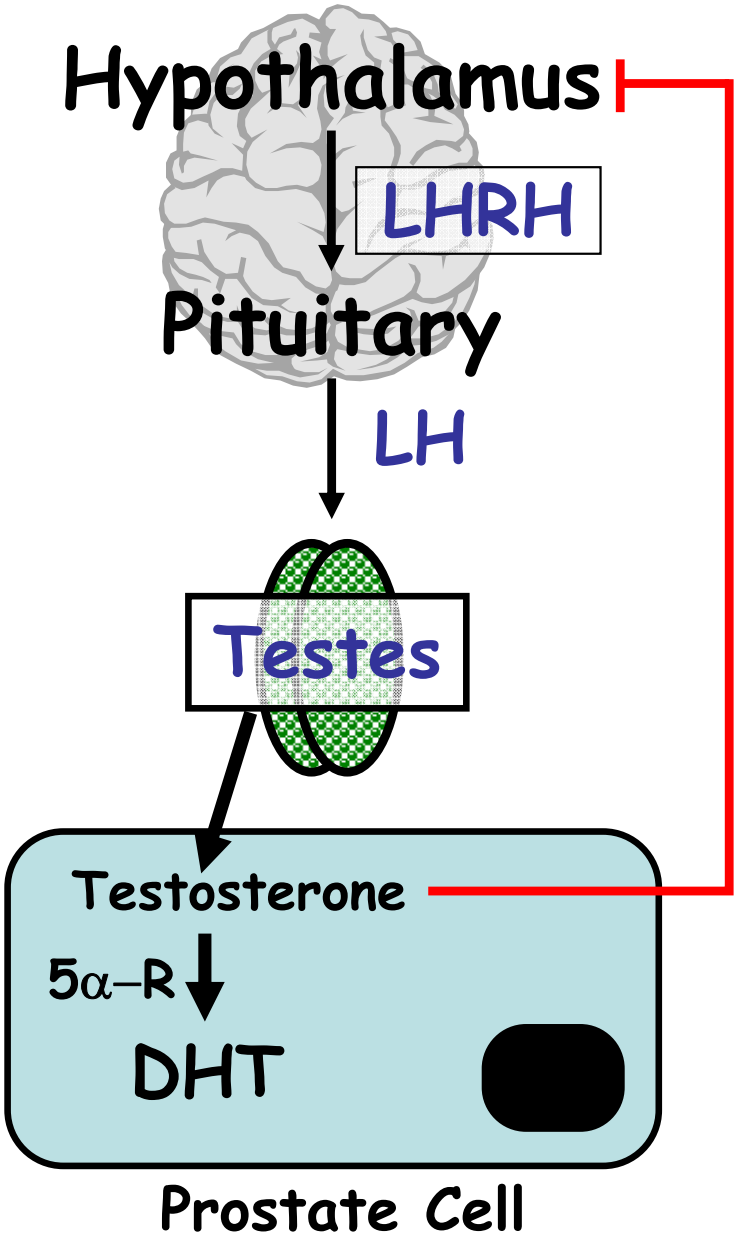
When No Androgens Are Present



Removing Androgens

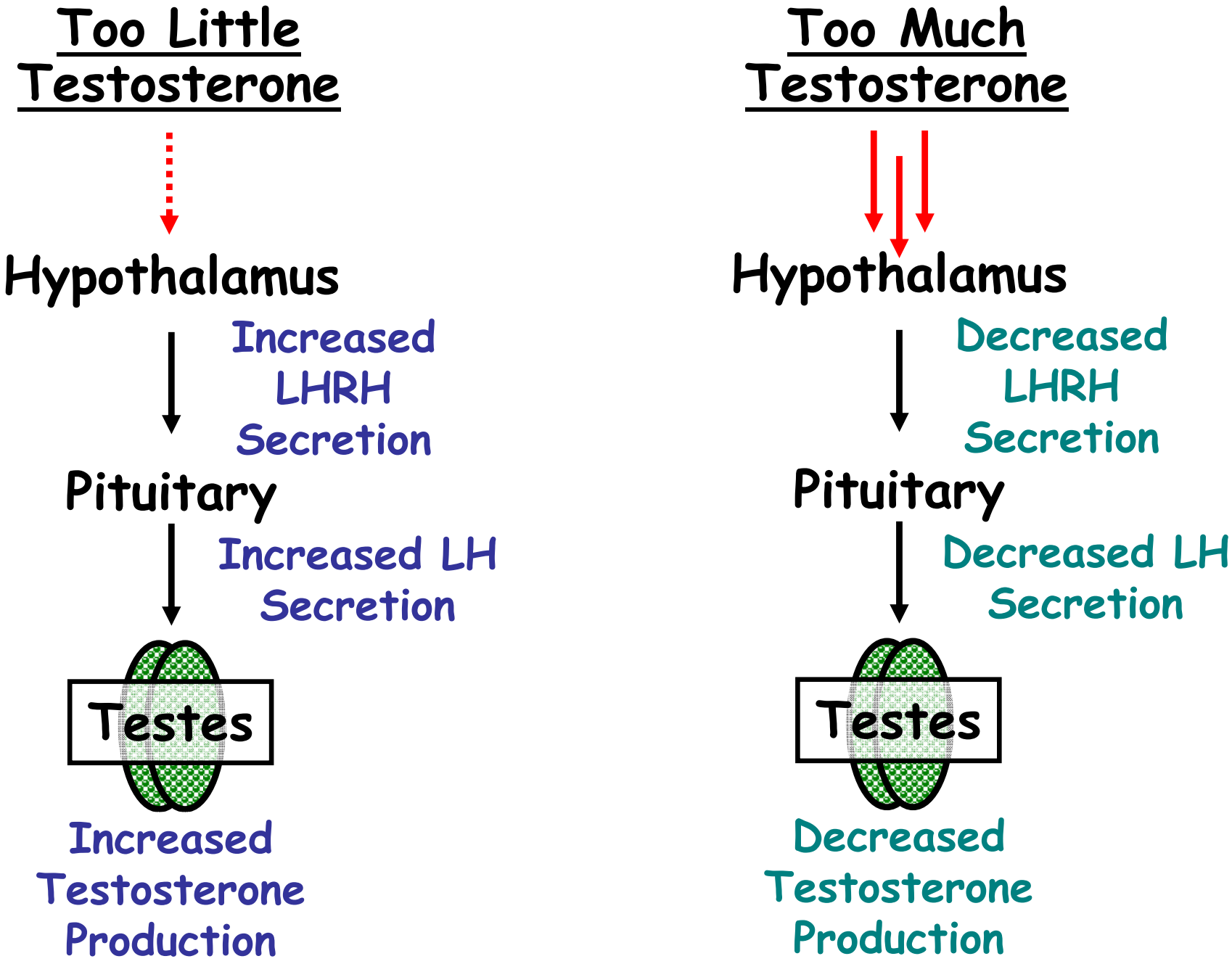
1. Orchiectomy (castration): surgical removal of the testicles.
2. Block testosterone **production**.
3. Block **conversion** to DHT.
4. Block the **effects** of testosterone.

Controlling Testosterone Production: Feedback

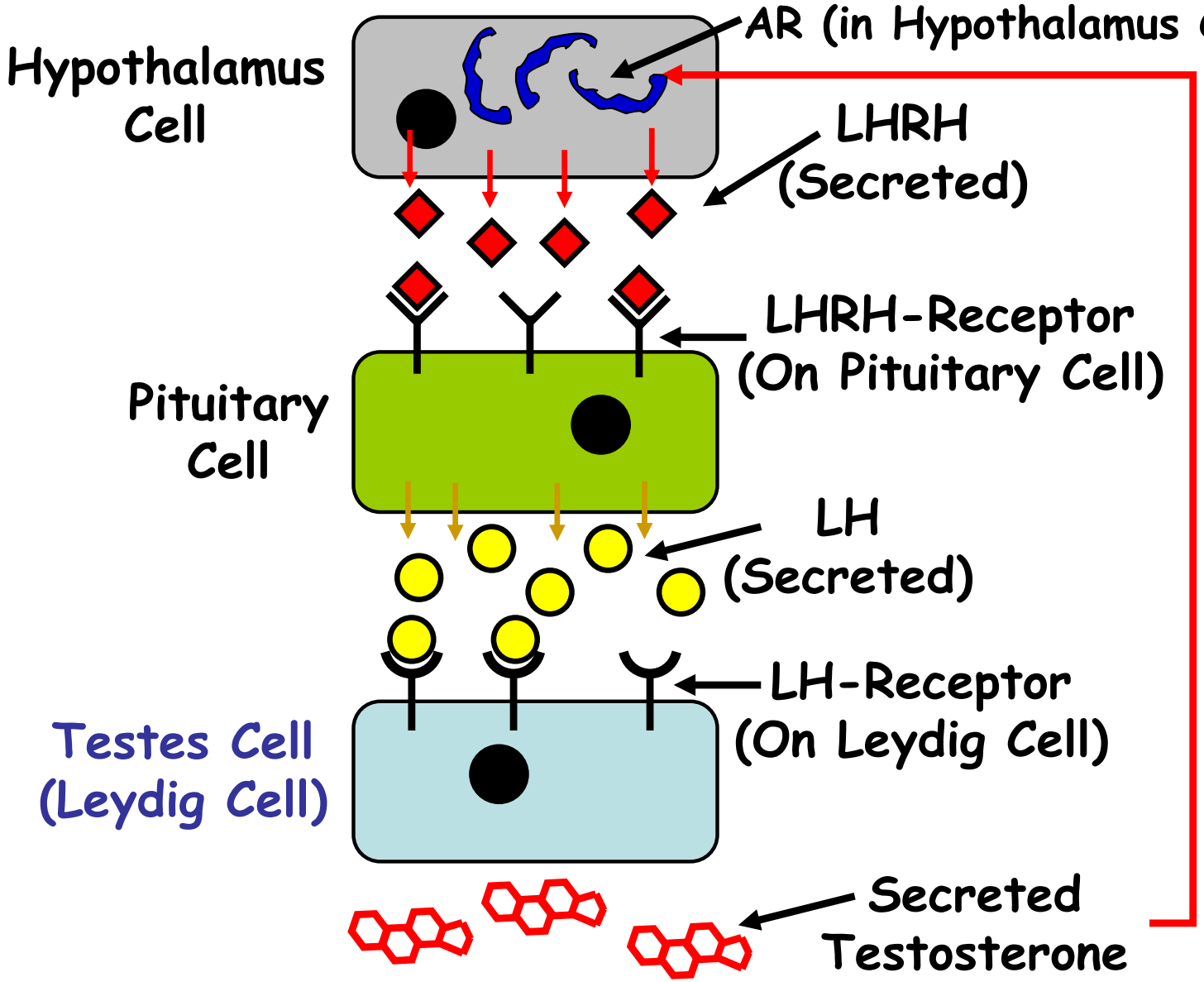


- Androgens circulate back to Hypothalamus and turn off LHRH production.
  - ✓Too much: less LHRH and less testosterone production.
  - ✓Too little: more LHRH and more testosterone production.
- Called "Negative Feedback".
- Important for maintaining constant levels of testosterone.

Negative Feedback: How Does it Work?



Receptors and Feedback

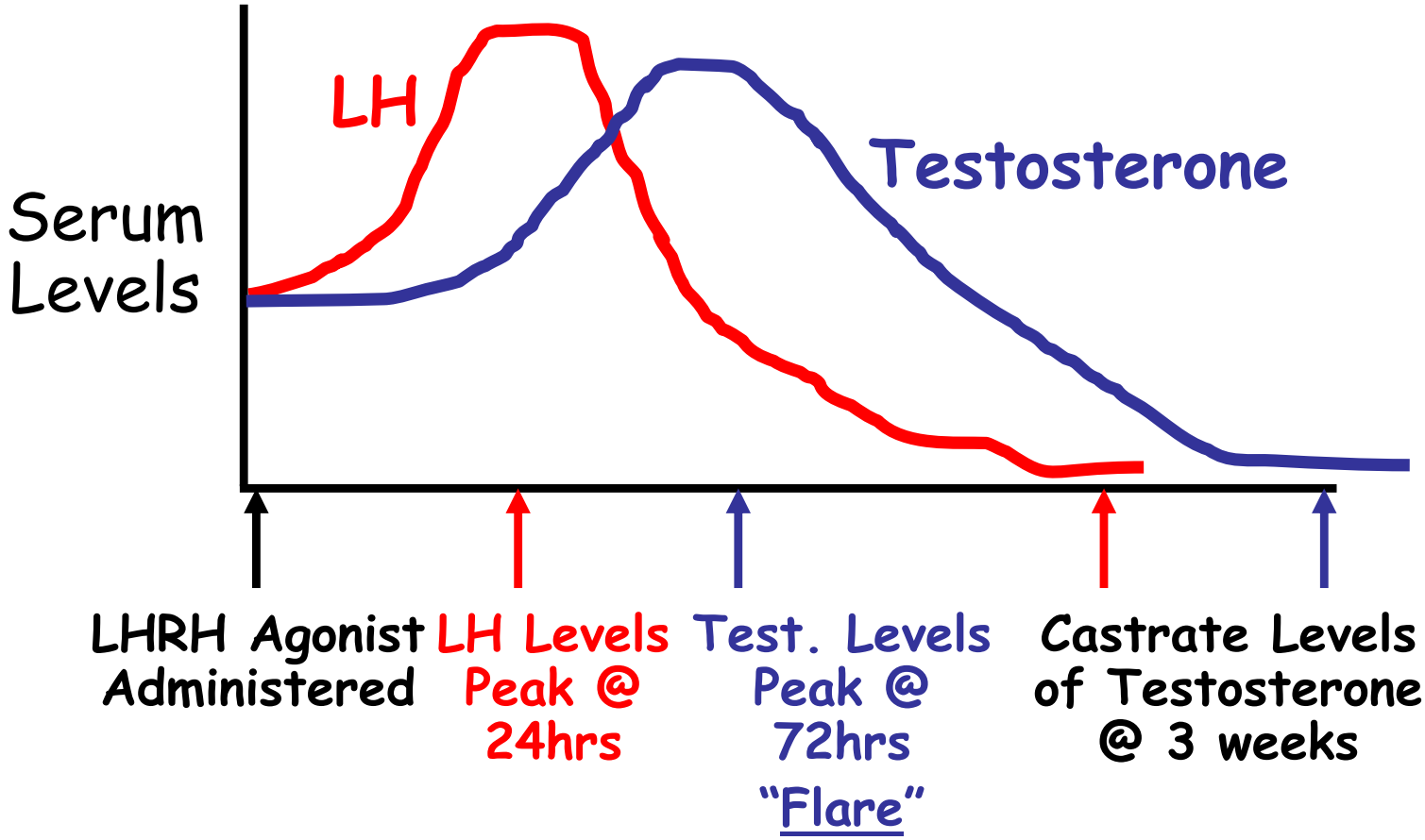


- Testosterone circulates back to hypothalamus and binds to Androgen Receptors in the hypothalamus cells.
- AR binding and activity modulates expression and secretion of LHRH.

LHRH Agonists

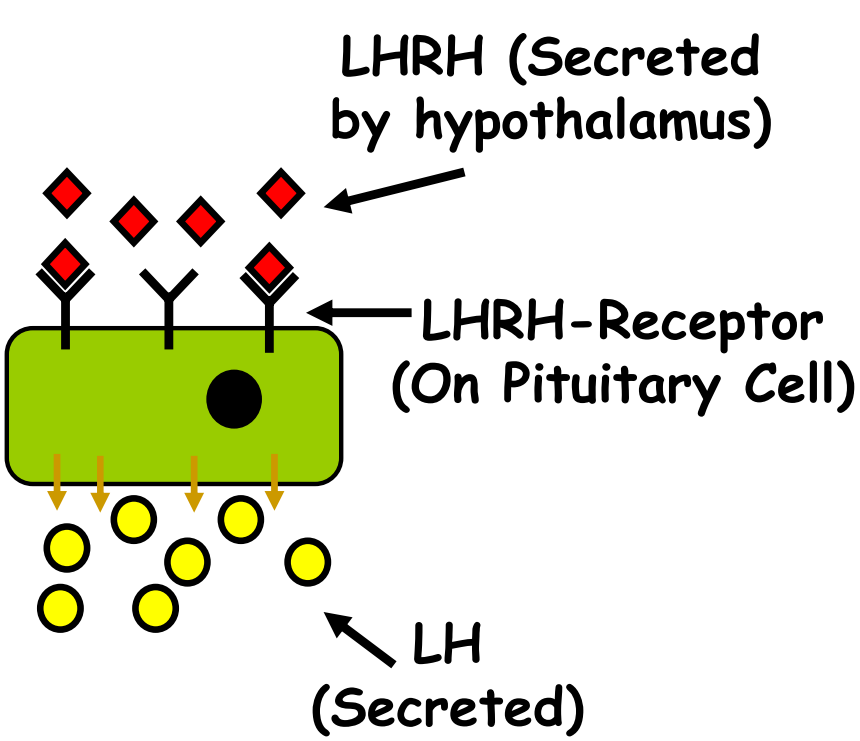
- An LHRH agonist is a factor that mimics the function of LHRH.
- Examples: Leuprolide (Lupron), Goserelin (Zoladex), Buserelin (Suprefact), and Nafarelin (Synarel).
- Chronic administration of LHRH agonists actually **inhibited LH secretion** resulting in lower testosterone levels.
- Same effect on prostate cancer metastases as estrogen, but without the cardiac side effects.
- Discovered by Andrew Schally, who was awarded the Nobel Prize in Medicine in 1977.

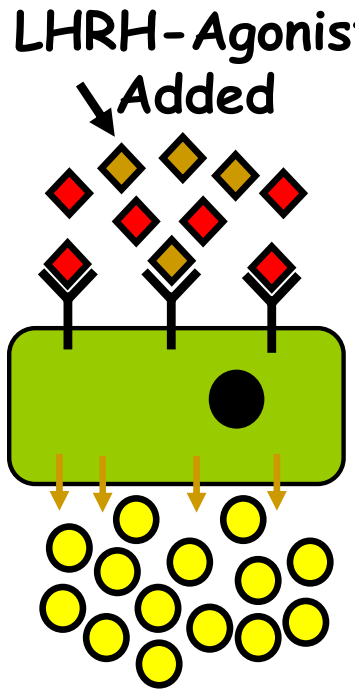
LHRH Agonists



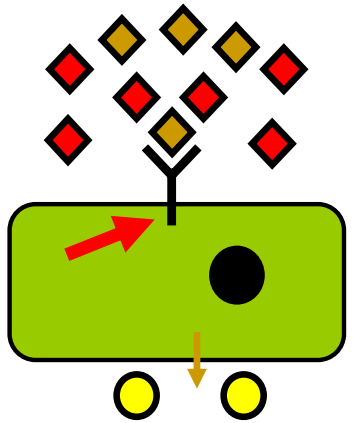
Not to scale.

How Do Chronic LHRH Agonists Decrease Testosterone?





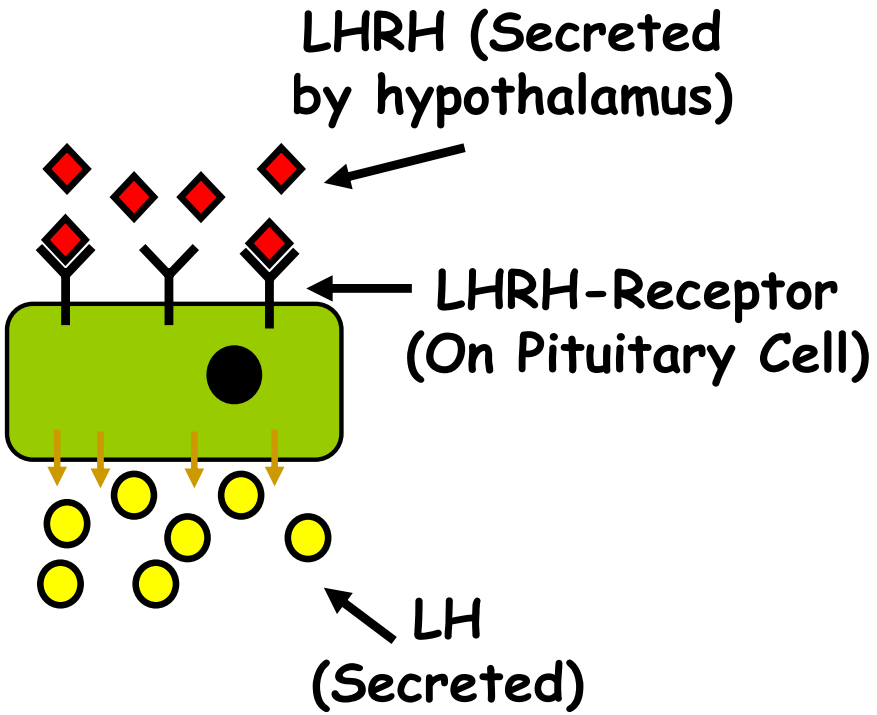
Initially:
Secreted Levels of LH Increase (Flare)

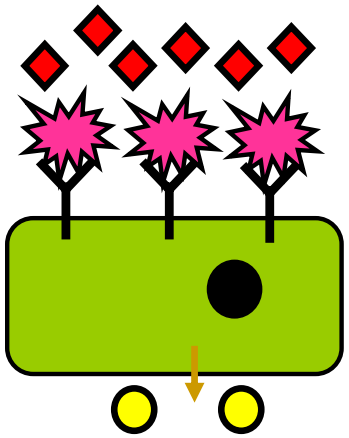


Chronically:
LHRH-Receptors disappear, LH secretion decreases (Castrate)

LHRH Antagonists

- An LHRH Antagonist is a factor that blocks the effect of LHRH.
- Examples: Cetrorelix (Cetrotide), Abarelix (Plenaxis), and Orgalutran (Ganirelix).
- Mechanism: directly inhibit the LHRH-receptor on Pituitary cells, resulting in decreased secretion of LH.

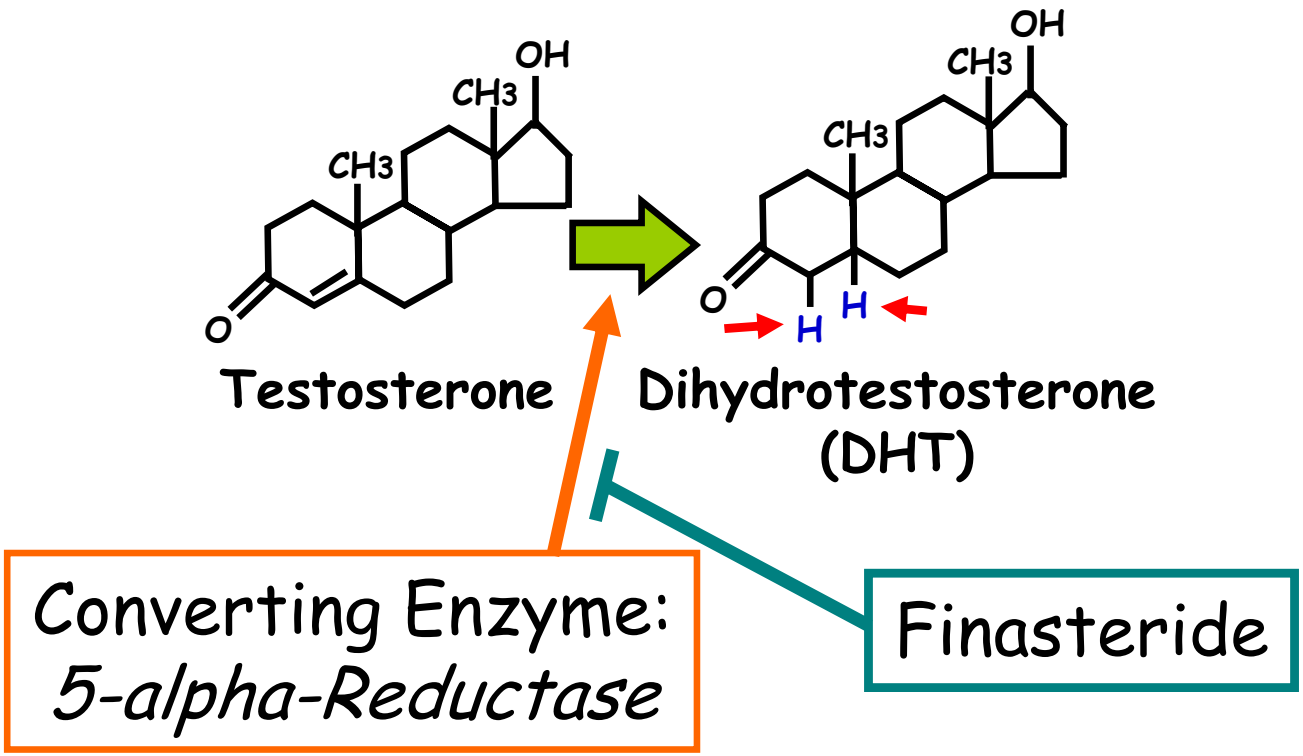




- LHRH-Antagonist prevents LHRH from binding to receptor.
- Decreased LH secretion and thus decreased testosterone production.
- No testosterone "flare"

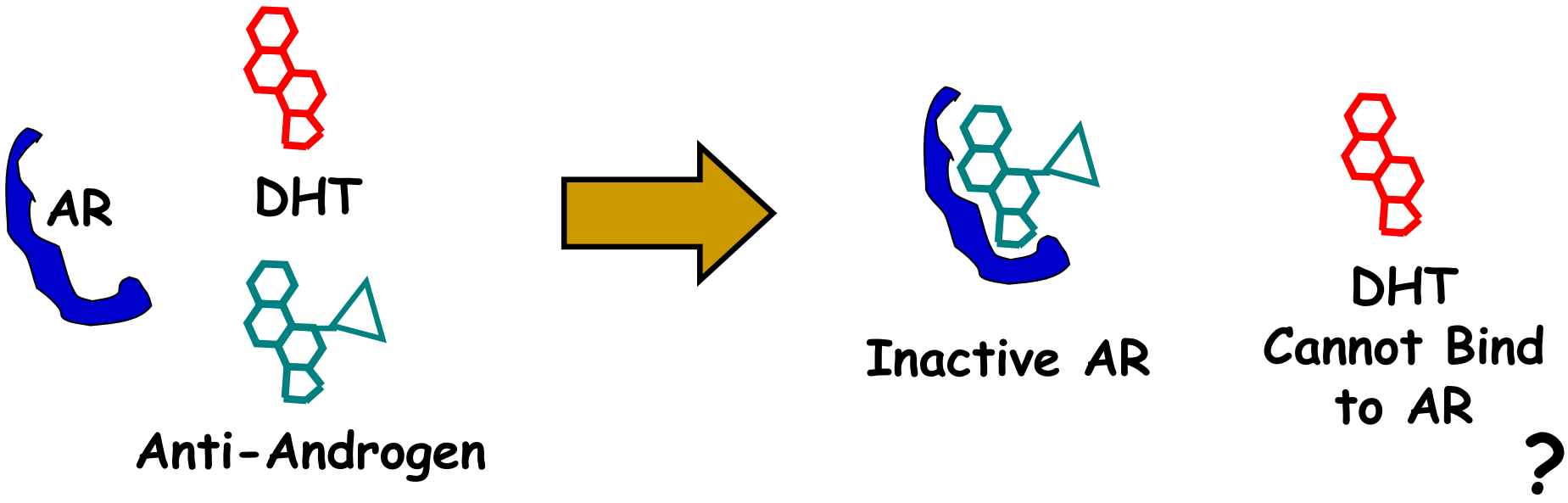
5α-Reductase Inhibitors

- Purpose: Block the enzyme that converts testosterone to DHT.
- Example: Finasteride (PROSCAR)
- Result: decreased Androgen Receptor activity.



Anti-Androgens

- Androgen "look-alike" molecules that bind to the Androgen Receptor and prevent binding of DHT (competite inhibition).
- Examples: Cyproterone (Cyprostat), Flutamide (Drogenil, Chimax) , Bicalutamide (Casodex), and Nilutamide (Nilandron).
- Bind and inhibit ARs in prostate as well as hypothalamus.



Hormone-Refractory Prostate Cancer (HRPC)

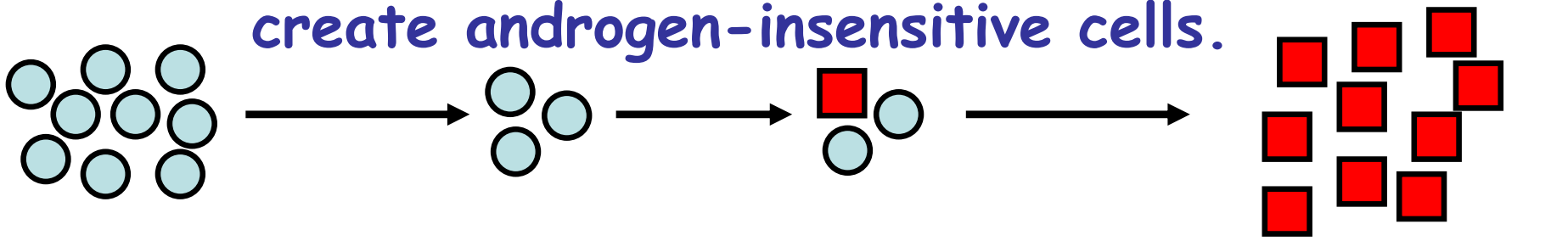
- Despite initial response rates of 80-90%, nearly all men treated for advanced prostate cancer develop hormone-resistant prostate cancer after 18-24 months.
- These "hormone-refractory" (HR) prostate cancer cells can grow in the absence of androgens.
- The behavior of HR prostate cancers differ widely between patients.
- Even Huggins noted in his seminal paper: "It is certain that, in many cases, regression of the neoplasm is not complete."

HRPC: Adaptive or Selective?

Androgen-Sensitive Prostate Cells

Androgen-Insensitive Prostate Cells

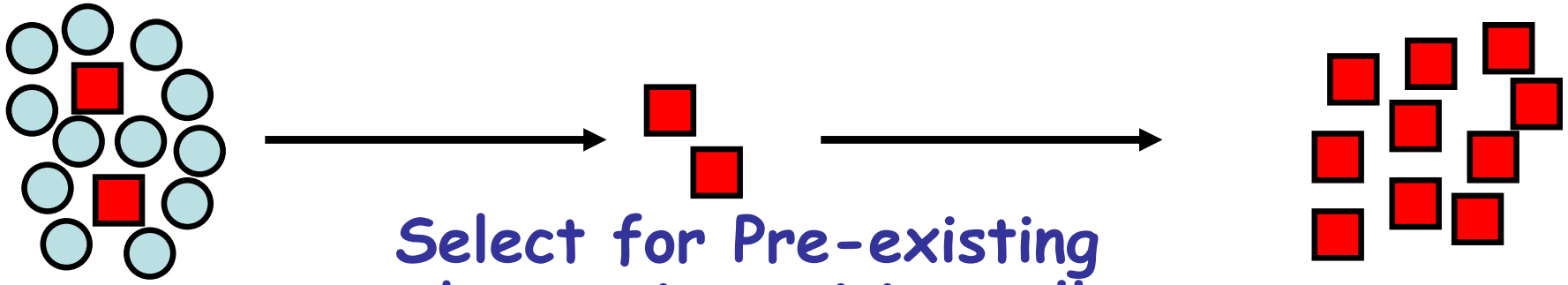
Adaptive: Gene and Protein changes create androgen-insensitive cells.



Hormone-Dependant Tumor

Tumor Regression

Hormone-Independent Tumor



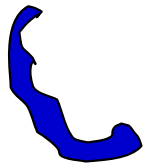
Select for Pre-existing androgen-insensitive cells.

What About Androgen Signaling?

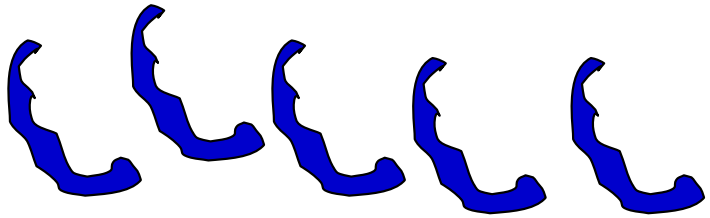
- In most cases, androgen-independent prostate cancer cells retain expression of the AR.
- Furthermore, AR activity is still crucial for the survival and growth of the prostate cancer cells.
- What happens? The prostate cancer cell seems to act through several molecular mechanisms to achieve AR function in the absence of testosterone.

HRPC: Mechanism #1
Amplification of the AR Gene

- Cancer cells by nature are genetically unstable.
- Thus, a prostate cancer cell can amplify and possess many copies of the AR gene.
- This results in over-expression of the AR and a much higher quantity of AR within a cell.
- As a consequence, these cells are **highly sensitive** to the low concentrations of circulating testosterone.



Normal Quantity of ARs

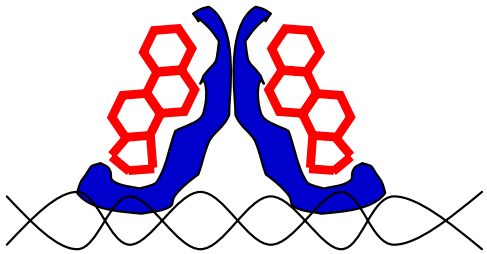


AR Gene Amplification and Protein Over-Expression

HRPC: Mechanism #2
Mutation of the AR

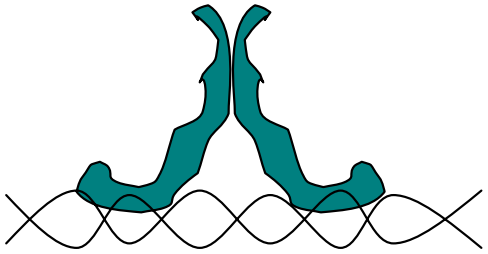
- Changes in the AR gene can result in activating mutations of the AR protein.
- As a consequence, the mutated AR can respond to other steroids or be activated without any steroid present.

Normal: AR requires DHT in order to bind DNA and activate gene expression



Androgen Response Element (ARE) on DNA

HRPC: Mutated AR can to bind DNA without DHT present



Androgen Response Element (ARE) on DNA

HRPC: Mechanism #3
Activation of AR Without DHT

- Some HRPCs contain non-mutated and non-amplified ARs.
- These ARs are abnormally over-phosphorylated from the activation of other growth signaling pathways.
- This can result in:
    1. DHT-independent activation of the AR.

    OR…

    1. The abnormal placement of AR within the nucleus.

HRPC: Mechanism #4
Change AR Co-Activators

- Co-Activators interact with and change the AR gene-expression complexes (Example: *ARA proteins).*
- Thus, significantly changing the quantity and activity of these Co-Activator proteins can allow for AR activity in the absence of testosterone.

What About Adrenal Androgens?

- Androstenedione accounts for ~5% of the total circulating androgens.
- Compounds are available that block the production of adrenal androgens.
- Examples: Aminoglutethimide (Cytadren) and ketoconazole(Nizoral).
- Inhibiting adrenal androgens have only a minor effect on prostate growth and prostate cancer.

Estrogen and Prostate Cancer

- As stated, estrogen can block the release of LHRH from the hypothalamus, leading to castrate levels of testosterone.
- Due to its significant cardiovascular side effects, estrogen is not commonly used today.
- However, data within the last decade suggests estrogen may effect prostate cancer cells directly.
- Normal and cancerous prostate cells express versions of the estrogen receptor (ERα and ERβ), and estrogen has been shown to block AR activity.
- More molecular and clinical research is clearly necessary to determine the role of estrogens in prostate cancer.

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Sources

1. A History of Prostate Cancer Treatment. Denmeade SR and Isaacs JT. Nature Reviews Cancer May 2002.
2. Litvinov IV et al.. Is the Achilles' Heel for Prostate Cancer Therapy a Gain of Function in Androgen Receptor Signaling? J of Clinical Endocrinology and Metabolism 88:2972; 2003.
3. McLeod DG and Thrasher JB. Initial hormone therapy for metastatic prostate cancer. UpToDate.com, 2004.
4. So A et al.. Mechanisms of the development of androgen independence in prostate cancer. World J of Urology, 2005 [Epub ahead of print].
5. The Molecular Biology, Endocrinology, and Physiology of the Prostate and Seminal Vesicles. Donald S. Coffey; Campbell's Urology 6th Edition.