Hormone Therapy for Prostate Cancer

Past, Present, and Future

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C. B. Huggins Dies at 95; Won Nobel for Cancer Work

By LAWRENCE K. ALTMAN

Dr. Charles B. Huggins, who won a Nobel Prize for discoveries that helped open the era of drug therapy for cancer and provide underpinnings of the modern treatment of prostate and breast cancer, died on Sunday at his home in Chicago. He was 95 and had been in failing health for several years.

Dr. Huggins started his career as a surgeon in the 1920's and made important findings in his specialty of urology at the University of Chicago before turning to cancer research in the 1930's. At that time cancers were generally treated by surgery and radiation but not drugs.

In 1941, Dr. Huggins published papers showing a relationship between the hormonal system and normal function of the prostate gland. By showing the competition between male and female hormones, and then selectively blocking their actions, he achieved initial successes in treating

Early successes in treating cancer with drugs.

cancer. Female sex hormones could be used to retard prostate cancer. The hormones, estrogens, were said to be the first drugs that when taken by mouth improved cancer. A similar effect could be achieved by surgically removing the testicles.

In the 1950's, Dr. Huggins went on to work on breast cancer. In 1966 he became the second surgeon to win a Nobel Prize in Medicine or Physiology. The Nobel Committee cited "fundamental discoveries concerning the hormone dependence of normal and neoplastic cells in experimental animals and their immediate practical application to the treatment of human prostatic and breast cancer." (Neoplastic cells are cancerous.)

The committee said Dr. Huggins's work had "already given many years of an active and useful life to patients with advanced cancer over the entire civilized world — patients who would have been lost to other forms of therapy."

Many experts criticized the Nobel Committee for waiting a quarter of a century to honor Dr. Huggins. But the Nobel Prize Dr. Huggins shared with Dr. Peyton Rous was only the second for cancer. The first was to Johannes Fibiger, whose research later turned out to be unfounded, and many felt the committee's mistake in 1926 contributed to the delay.

Dr. Huggins had turned 65 just before winning the Nobel Prize. When asked about retiring, the man who described himself as a workaholic said, "The cancer problem isn't licked yet!" The University of Chicago then extended his contract.

Dr. Huggins's research changed understanding of the behavior of all cancer cells by showing that they were not autonomous and self-perpetuating, as previously believed, but were dependent on hormones and other chemical signals to grow and survive. By depriving cancer cells of such signals Dr. Huggins showed that the spread of cancer could be retarded, at least temporarily, and the patients' health could be restored. That finding greatly stimulated cancer research.

Dr. Huggins performed his own experiments, worked directly with animals, strove to avoid administrative responsibilities and intentionally ran a small laboratory. "Discovery is for the single mind, perhaps in company with a few students," he said. He told colleagues: "Don't write books. Don't teach hundreds of students. Discovery is our business. Make damn good discoveries."

Charles Brenton Huggins was born in Halifax, Nova Scotia, on Sept. 22,

University of Chicago

Dr. Charles B. Huggins in 1966, when he won a Nobel Prize.

1901. He earned a medical degree from Harvard University in 1924 at the age of 22 and trained in general surgery at the University of Michigan.

Then, with no formal training in research or urology, he became a founding faculty member of the University of Chicago. In 1936 he became a full professor. He is credited as a pioneer in understanding the physiology and biochemistry of the male urological and genital tract and for bringing a new level of scientific inquiring to the neglected surgical specialty of urology.

Dr. Huggins applied his surgical skills to do what Science magazine called "an ingenious" operation on dogs. He used it to do research that improved the understanding of the role of chemicals and hormones on the prostate gland. In 1944, he performed the first complete removal of the adrenal glands as a drastic therapy for advanced cancer.

In 1949, Dr. Huggins stumbled. He reported developing a simple blood test to detect cancer in its earliest stages. But the test quickly proved unreliable.

In 1950, he turned to breast cancer, advancing findings made in the late 1890's that removal of the ovaries could benefit the course of cancer for some women. In 1951, he showed that breast cancers were also dependent on specific hormones. He showed that when he removed the sources of those hormones, the ovaries and adrenal glands, he could cause substantial regression of advanced breast cancers in 30 percent to 40 percent of treated women.

But there was no way to predict which women would benefit from such endocrine surgery. So he urged a colleague, Dr. Elwood V. Jensen, to develop a method to identify the estrogen-receptor content of breast cancers and to use that to predict response to hormone therapy. Now all breast cancers are classified as estrogen-receptor positive or negative, an important guide to prognosis and therapy, and medications like tamoxifen that can block the effects of estrogen have become important tools in treating breast cancer.

Dr. Huggins also discovered that a single injection of a chemical could quickly produce breast cancers in certain types of rats. The experimental models are known as "Huggins tumors."

In describing the thrill of discovery, Dr. Huggins said: "That night I walked home, one mile, and I had to sit down two or three times, my heart was pounding so. I thought, this will benefit man forever. A thousand years from now people will be taking this treatment of mine."

Dr. Huggins is survived by a daughter, Emily Fine, of San Francisco. His wife, Margaret, died in 1983, and a son, Dr. Charles Edward Huggins, who developed a method for freezing and thawing donated blood so it can be stored almost indefinitely, died in 1989.

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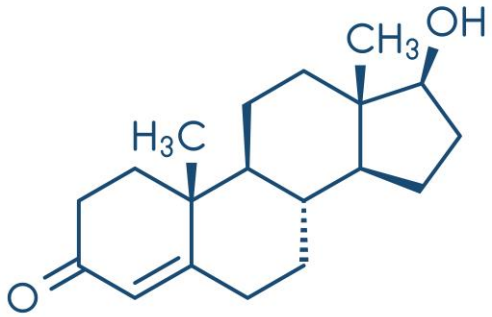
Observation

- Prostate cancer (temporarily) goes away when deprived of testosterone

Questions

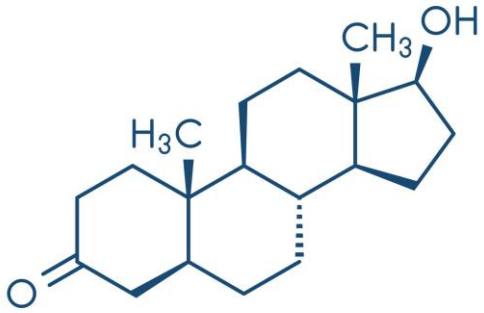
- What is testosterone?
- Where and how is testosterone made?
- How does testosterone work?
- Why is the benefit of testosterone deprivation only temporary?
- How can we use this knowledge about testosterone to design effective treatments?



testosterone

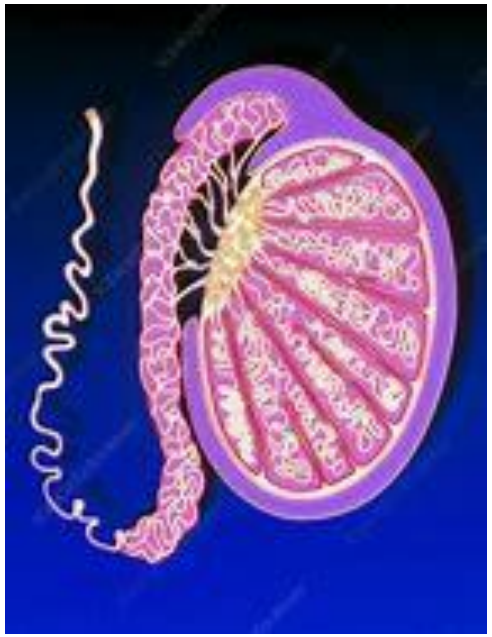
5 alpha reductase

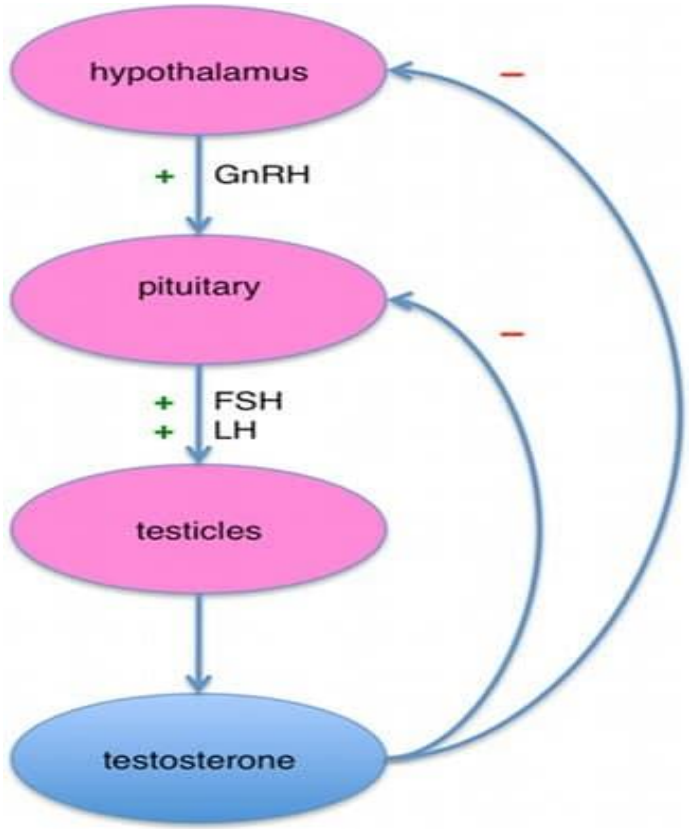
Finasteride
Dutasteride
Saw palmetto



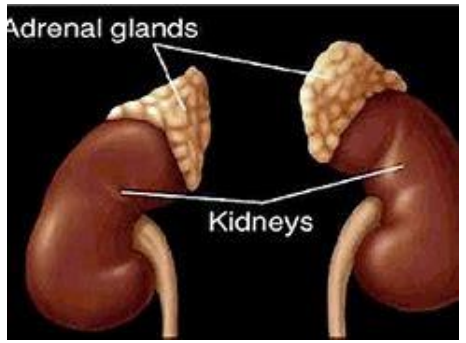
dihydrotestosterone

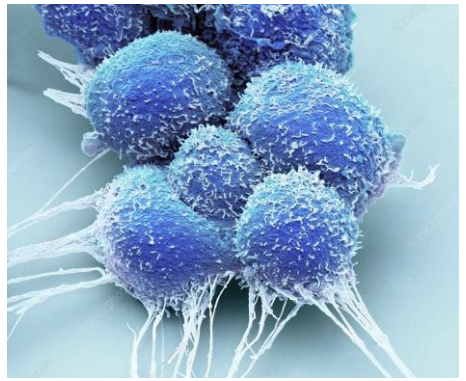
90%



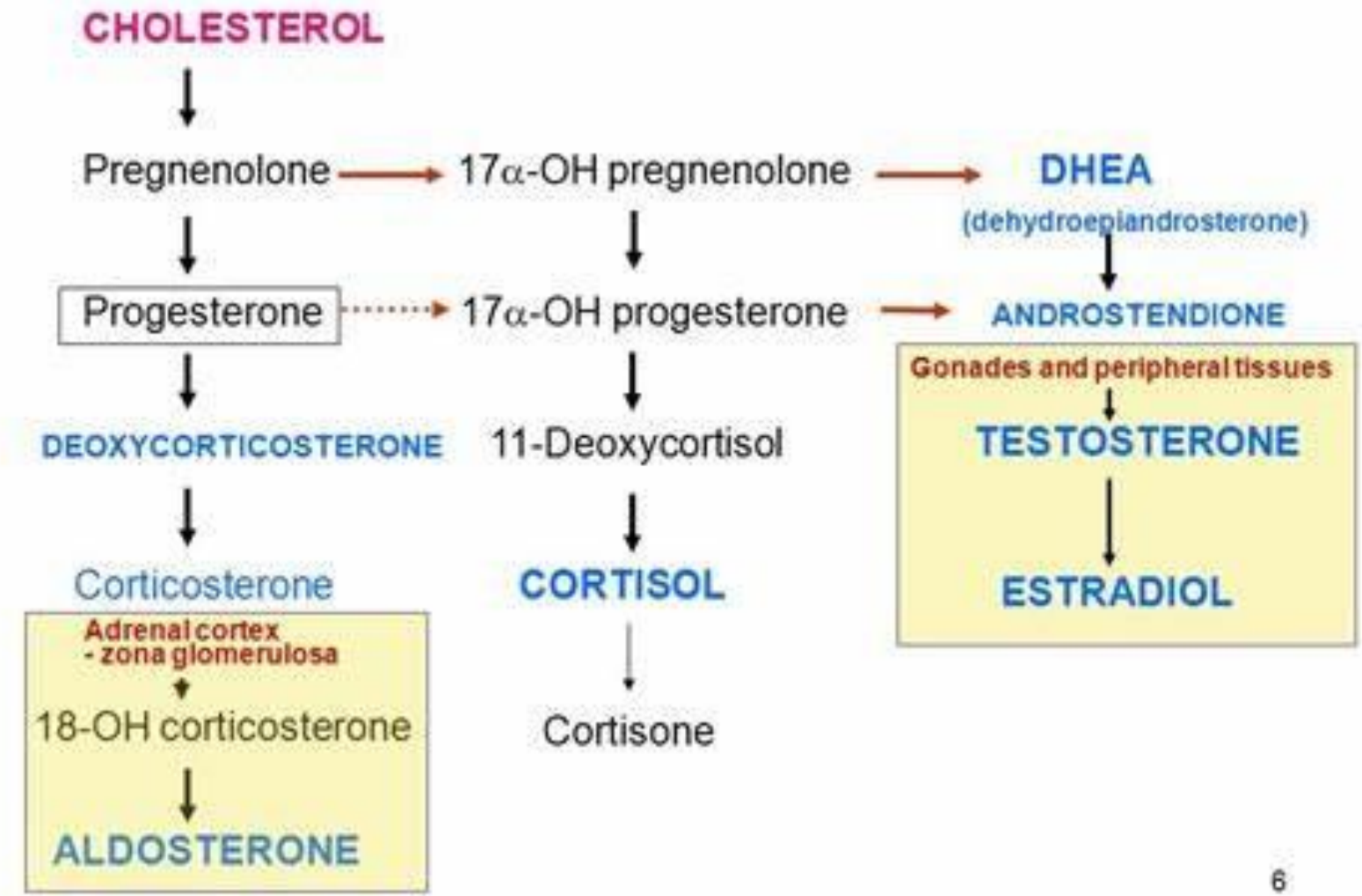


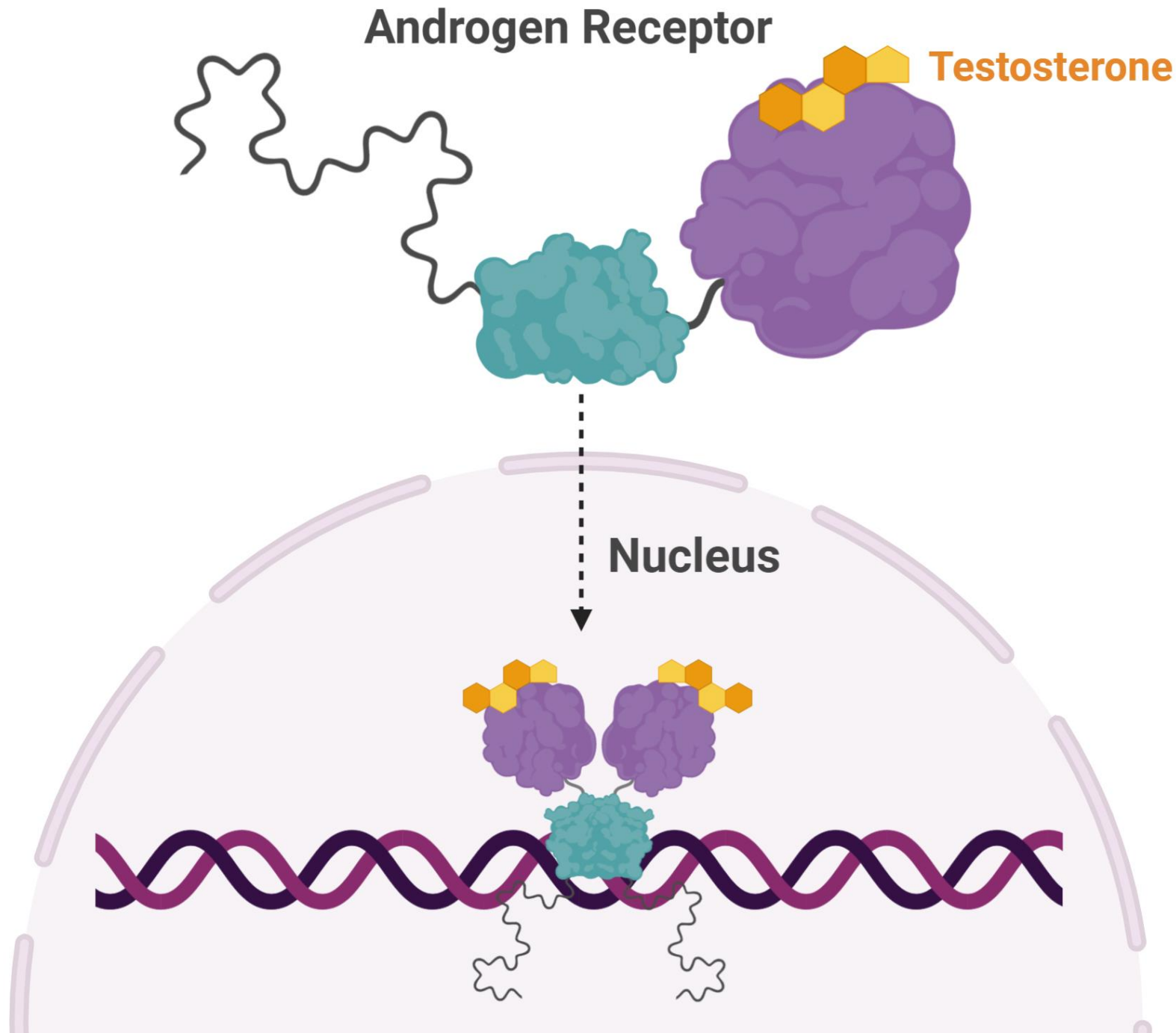
10%

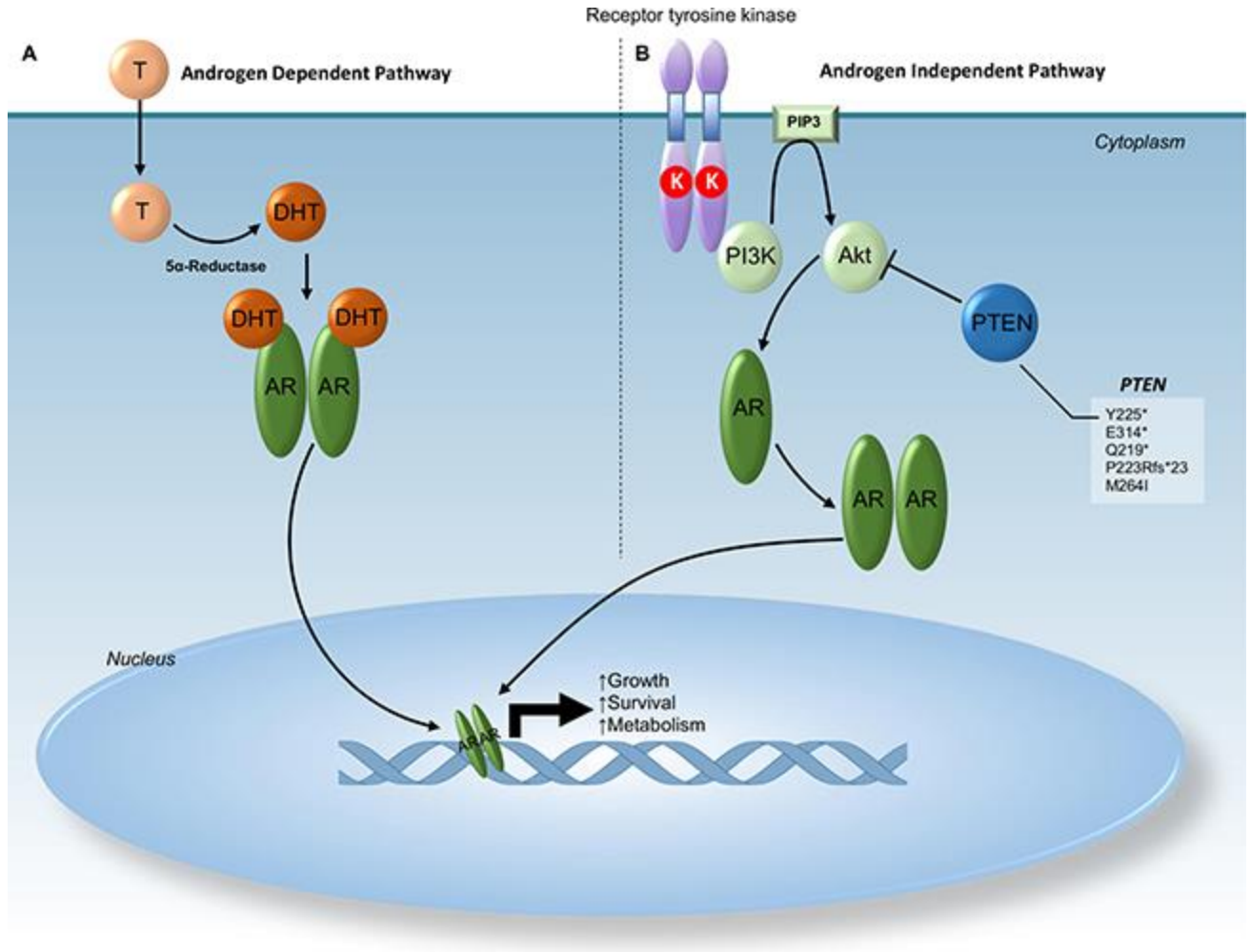




Steroidogenesis




Androgen Receptor
Testosterone
Nucleus


A
T
Androgen Dependent Pathway
T
DHT
5α-Reductase
DHT
DHT
AR
AR
Receptor tyrosine kinase
B
Androgen Independent Pathway
PIP3
Cytoplasm
K
K
PI3K
Akt
PTEN
PTEN
Y225*
E314*
Q219*
P223Rfs*23
M264I
AR
AR
AR
Nucleus
↑Growth
↑Survival
↑Metabolism

Hormone Treatment Strategies for CaP

Pre-1985

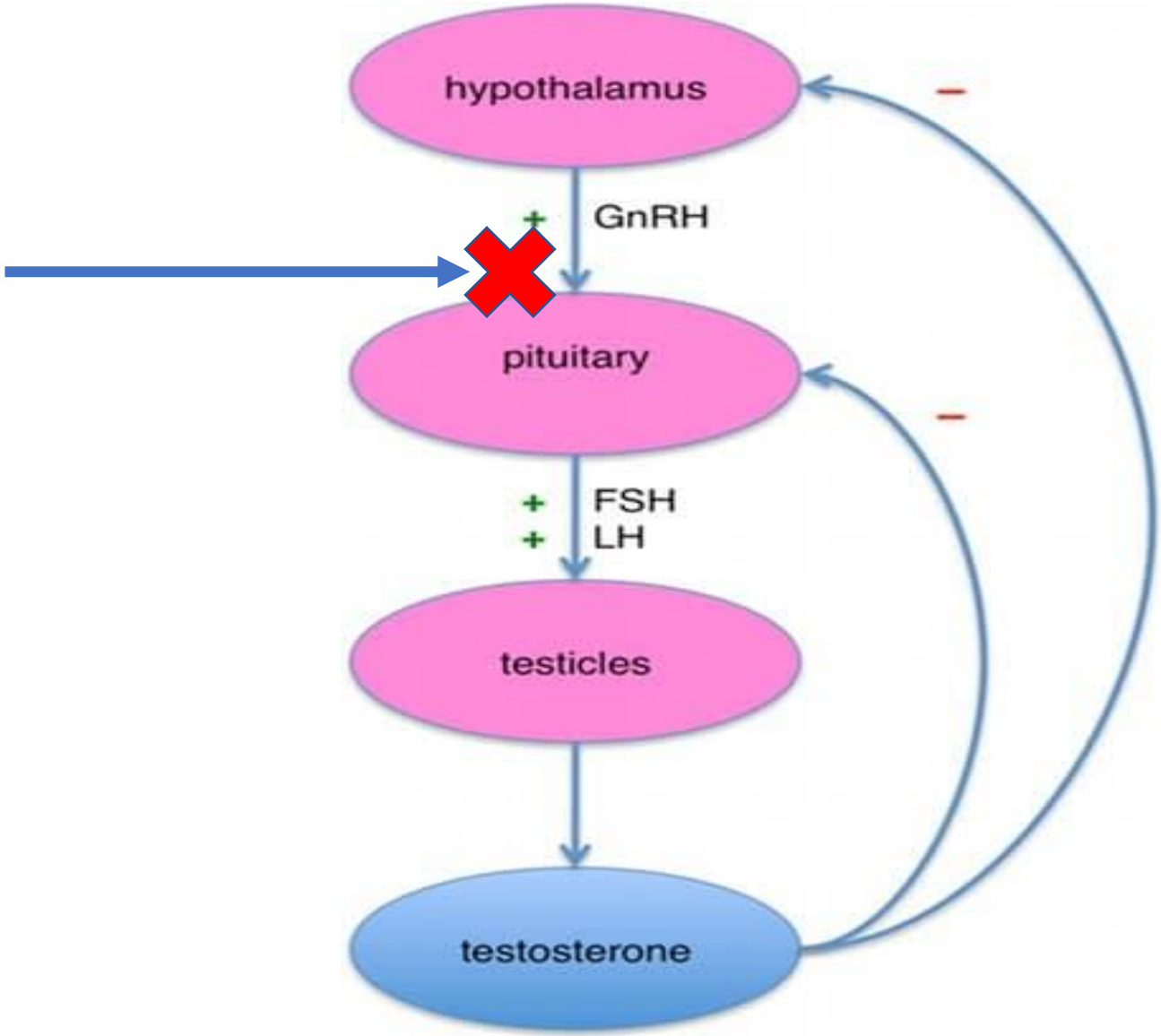
- Surgery to remove testosterone source

Post-1985

- Medically block the body's ability to produce testosterone
- Medically block the androgen receptor from functioning

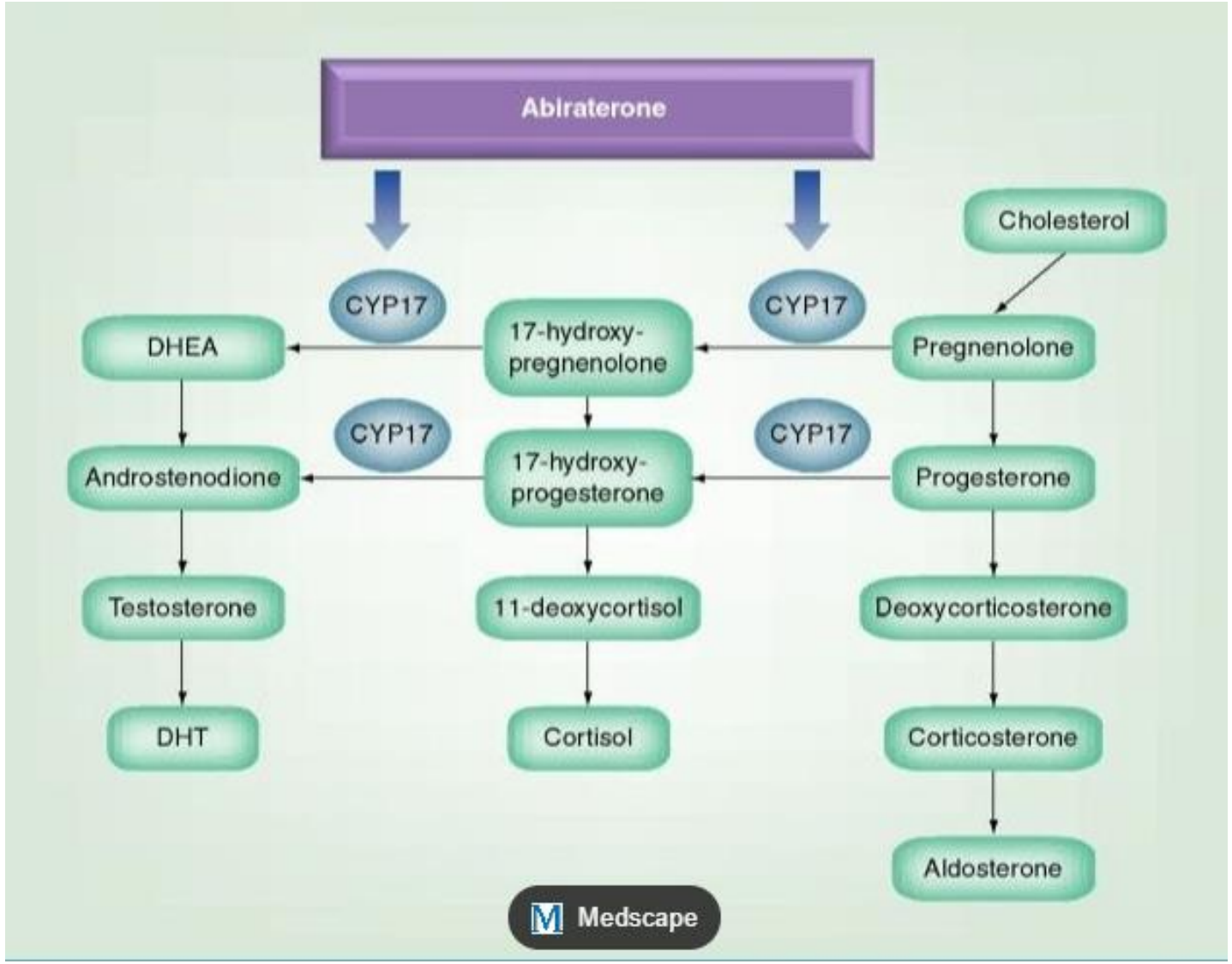
Agents That Block Testicular Function

Leuprolide
Goserelin
Triptorelin
Degarelix
Relugolix

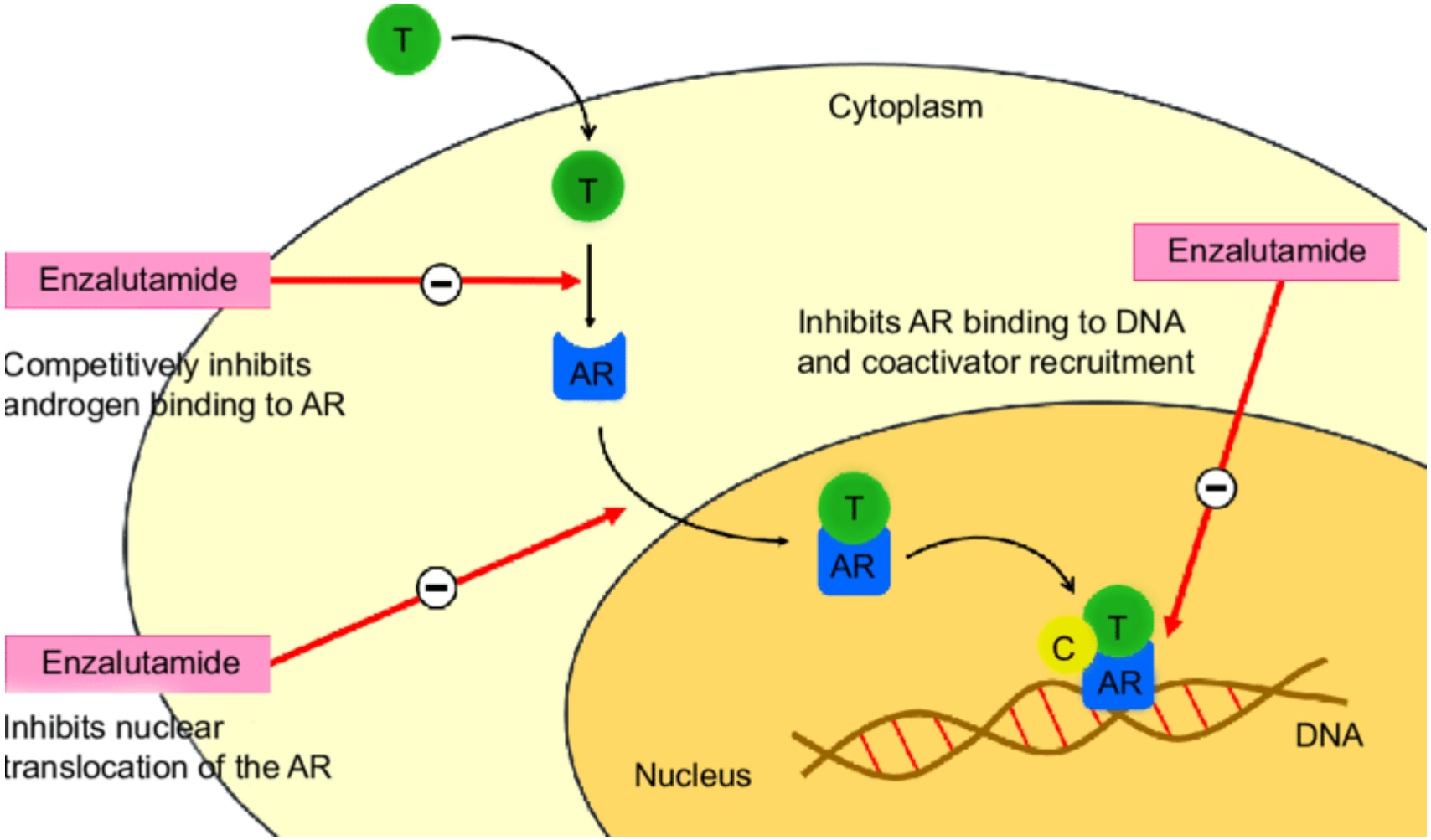


Adrenal and cancer cell production of testosterone unaffected by these agents

Blocking Testosterone Biosynthesis



Inhibitors of the Androgen Receptor



First Generation

- Flutamide
- Nilutamide
- Dicalutamide

Second Generation

- Enzalutamide
- Apalutamide
- Darolutamide

FDA Approvals for Hormonal Therapies

1985: Leuprolide (GnRH Agonist)

2008: Degarelix (GnRH antagonist)(CS21)

2011: GnRH agonist + Abiraterone (COU301, COU302)

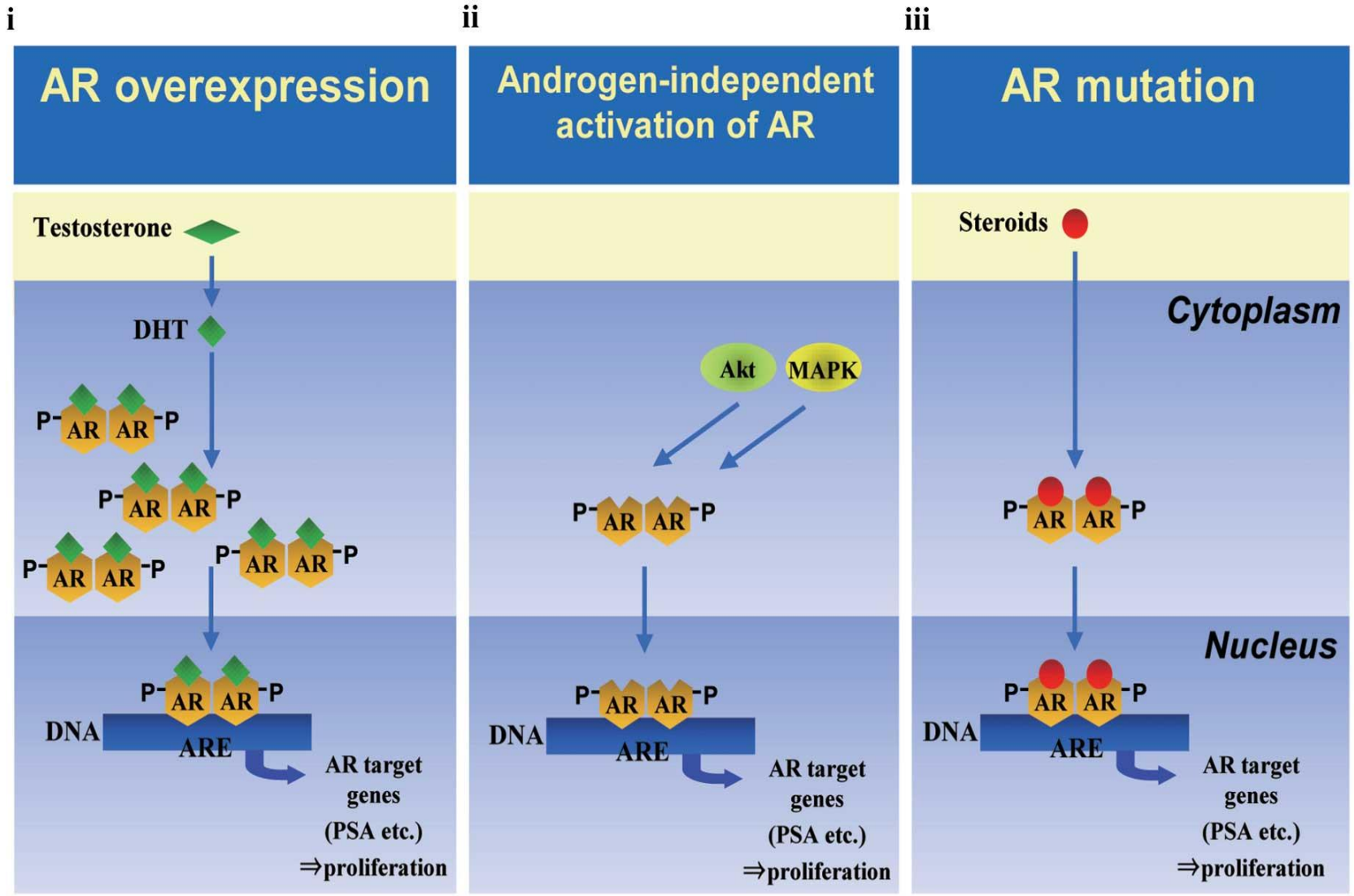
2012: GnRH agonist + Enzalutamide (PREVAIL, AFFIRM)

2018: GnRH agonist + Apalutamide (SPARTAN)

2019: GnRH agonist + Darolutamide (ARAMIS)

2020: Relugolix (GnRH antagonist) (HERO)

Mechanisms of Resistance to Anti-Androgen Therapy



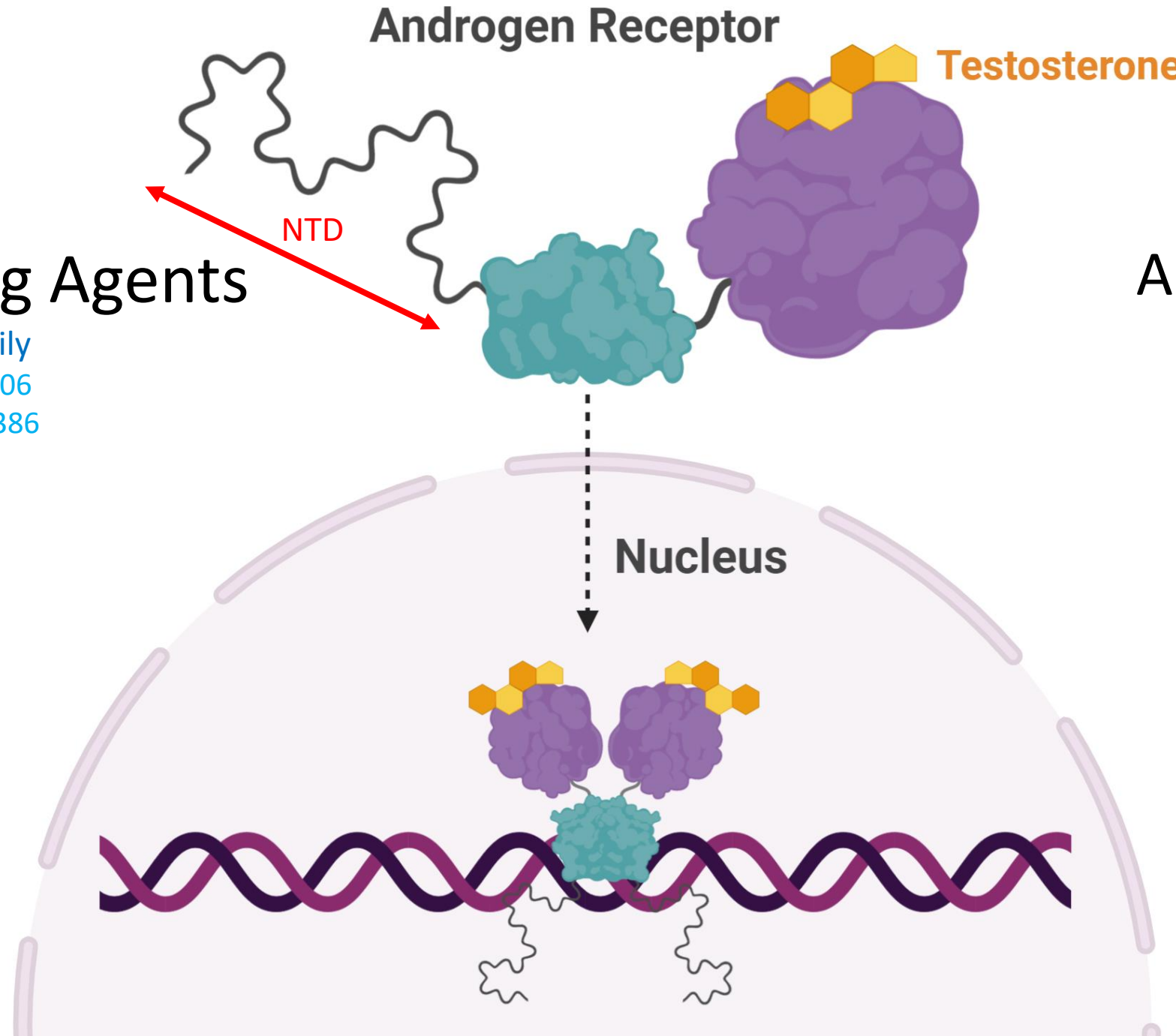
Some AR Mutations and their Consequences

Mutation	Consequences of Alteration
T877A	AR activated by estrogen, progesterone, resistant to enzalutamide
L701H	AR activated by cortisol, cortisone
F876L	AR resistance to enzalutamide and apalutamide
AR-V7	AR loses LBD, permanently in active mode, resides in nucleus
AR-V567es	AR loses LBD, permanently in active mode, resides in nucleus

NTD Binding Agents

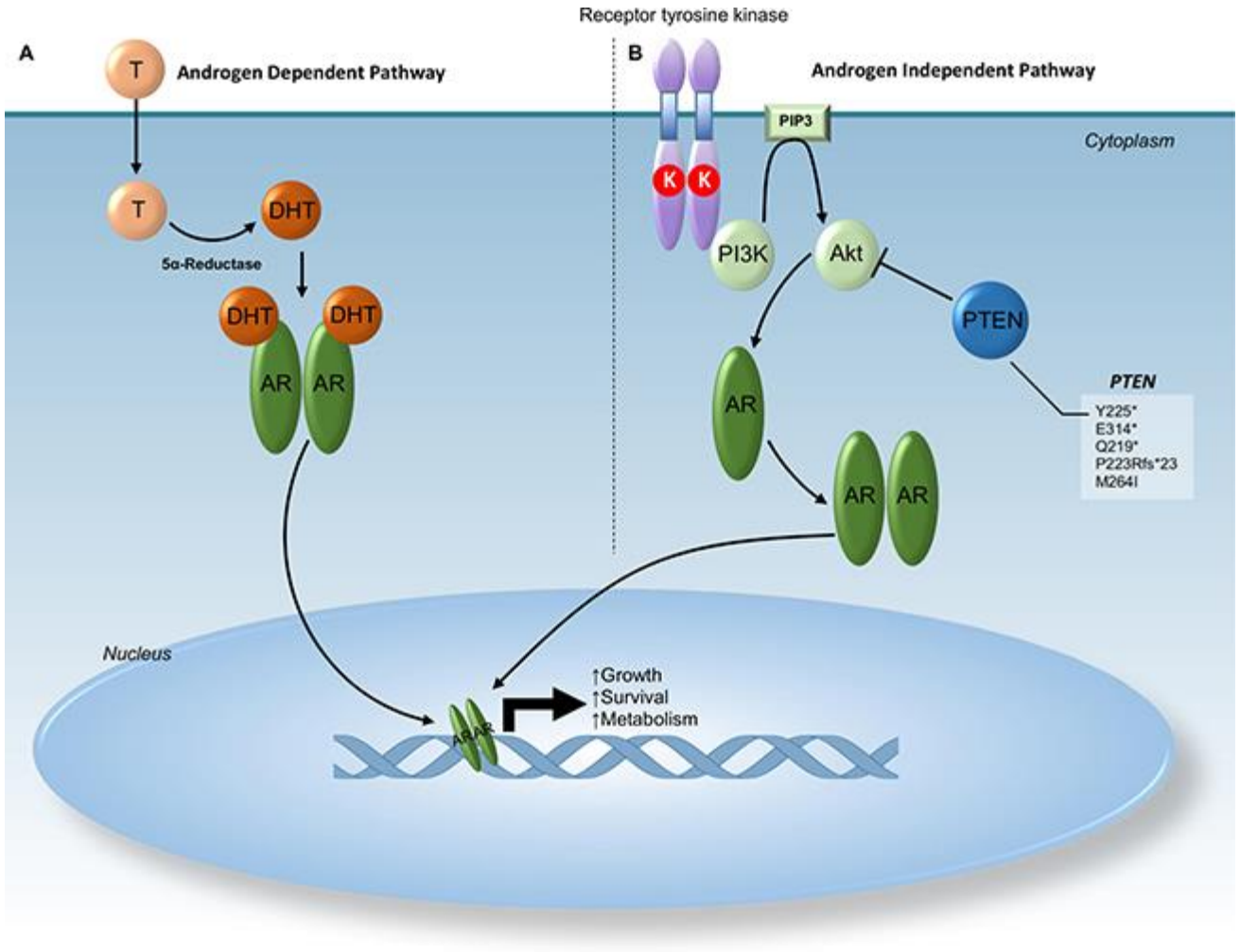
EPI family

- EPI-506
- EPI-7386



AR Degraders

Galaterone
ARV-110
ARCC-4
AZD3514



Drugs That Block Pi3K/Akt Signaling Pathway

Ipatasertib

Capivasertib (AZD5363)

Afuresertib