

“From Androgen Receptor Ligand Discovery to Potential Therapeutic Uses”

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Thanks

Sarah Ashley Block, *Director* | Office of Research
Communications & Marketing

Department of Pharmaceutical Sciences (Staff)

Brenda Thornton (Retired)

Corliss Finlay

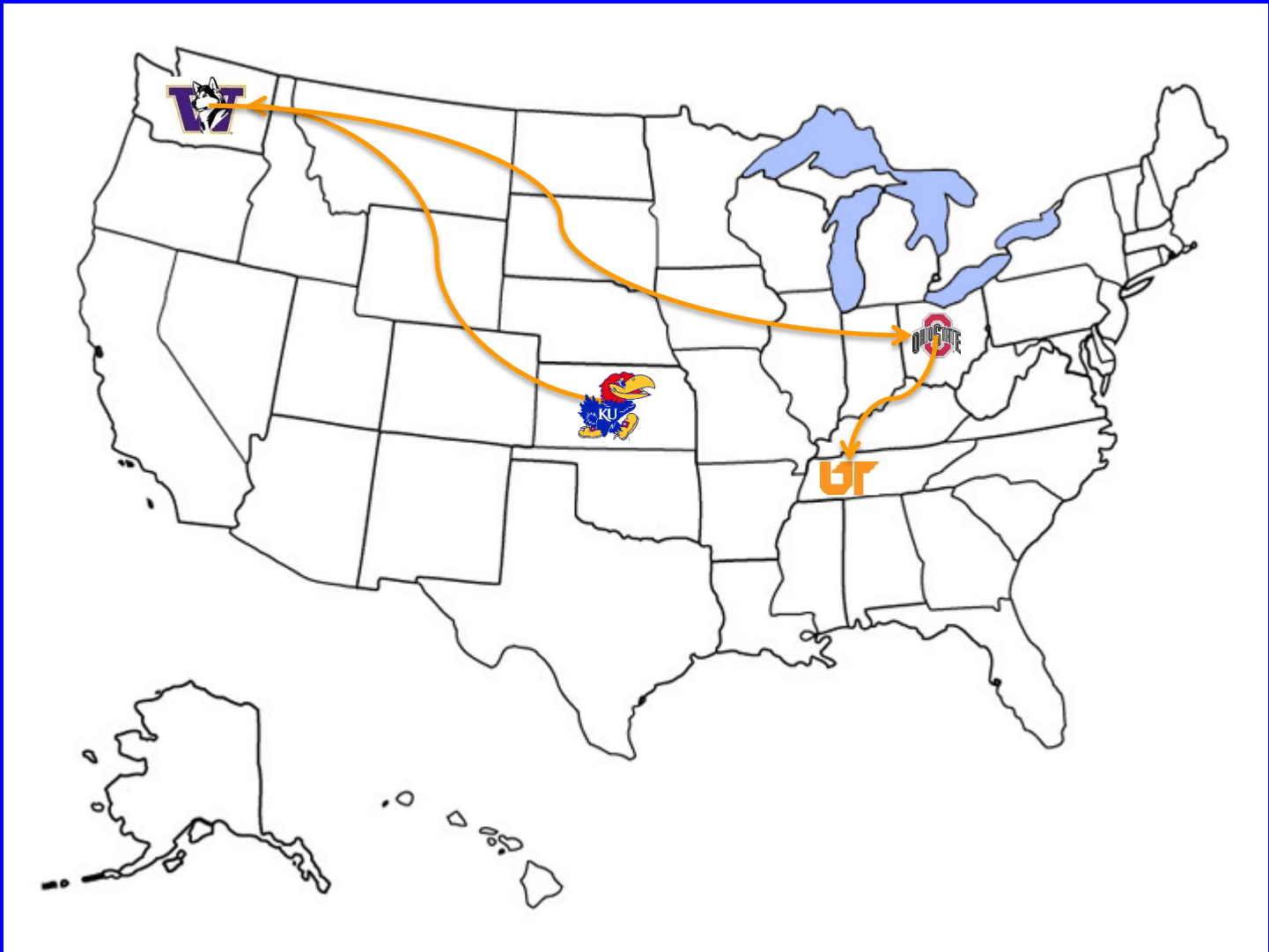
Shelley Renee Cannioto

Lisa L. Schaffer

David Clark

“No beauty shines brighter than a good heart” by

Alyssa Witte





James T. Dalton

“increased vigor and capacity for work”

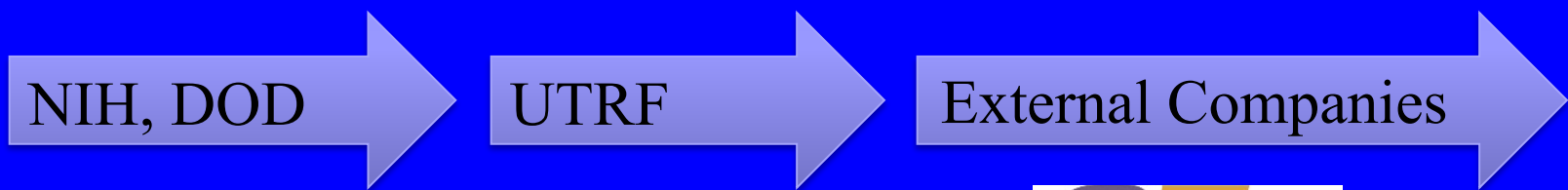
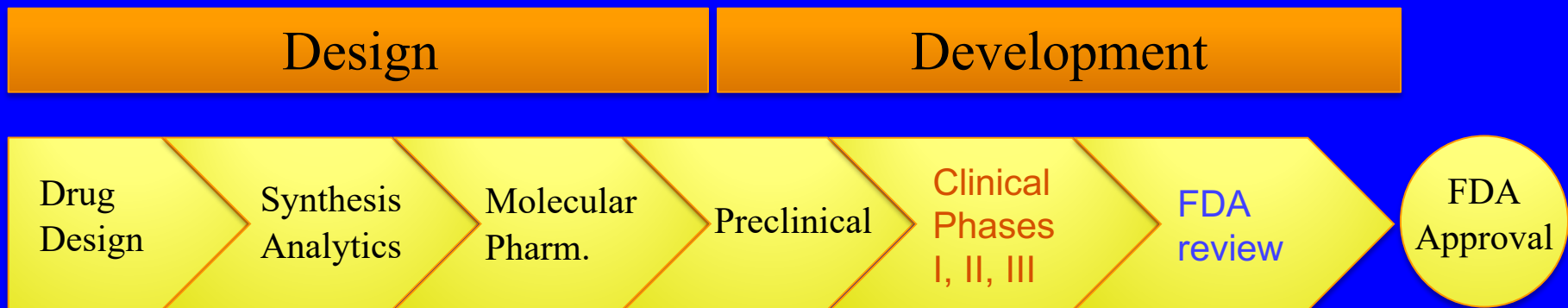
Professor
BROWN SEQUARD'S
Method
EXTRACTS OF ANIMAL ORGANS.
Testicle Extract,
Grey Matter Extract,
Throid Gland Extract, &tc., &tc.
Price for 25 Injections, \$2.50.
New York Biological and Vaccinal Institute
Laboratory of Bovine Vaccine and of Biological Products

CE Brown-Sequard. CR Seanc Soc Biol (1889): 1: p 420.

I am very fortunate because I can tell you about a drug we synthesized and discovered in our laboratory--- Unfortunately you can buy it on the Internet (Illegal).

It will increase your muscle for sure and should increase your capacity for work or whatever physical activity you would like.





Veru

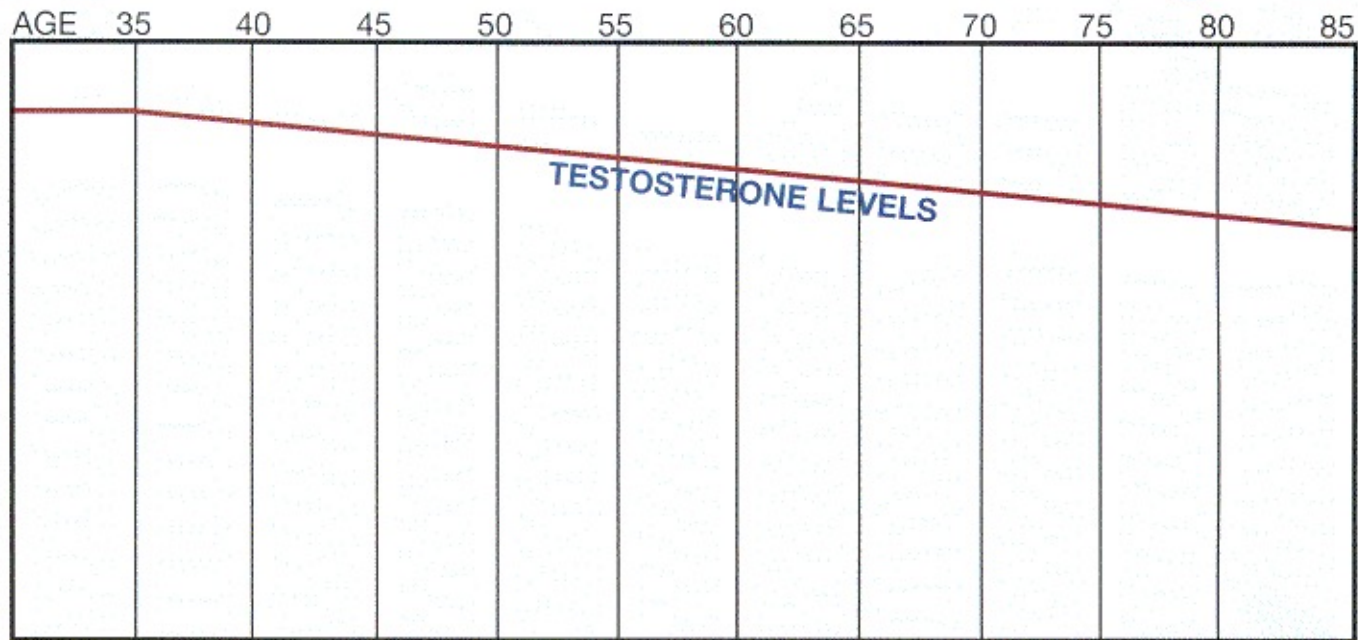
RxBio Inc

EDLabs

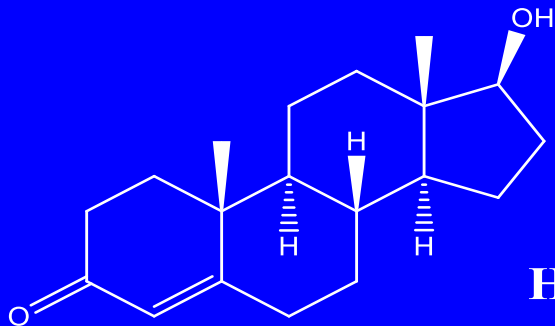


Molecular Design International

Testosterone Levels Relative To Age



The level of testosterone in your body steadily declines about .5% to 2.0% per year from the age of 35.



TESTOSTERONE
Below 150 ng/dL

Concern

ADAM (Androgen Decline Aging Males)

Andropause

Treat

Hormone Replacement Therapy (HRT)

alternative

**Selective Androgen Receptor
Modulators (SARMS)**



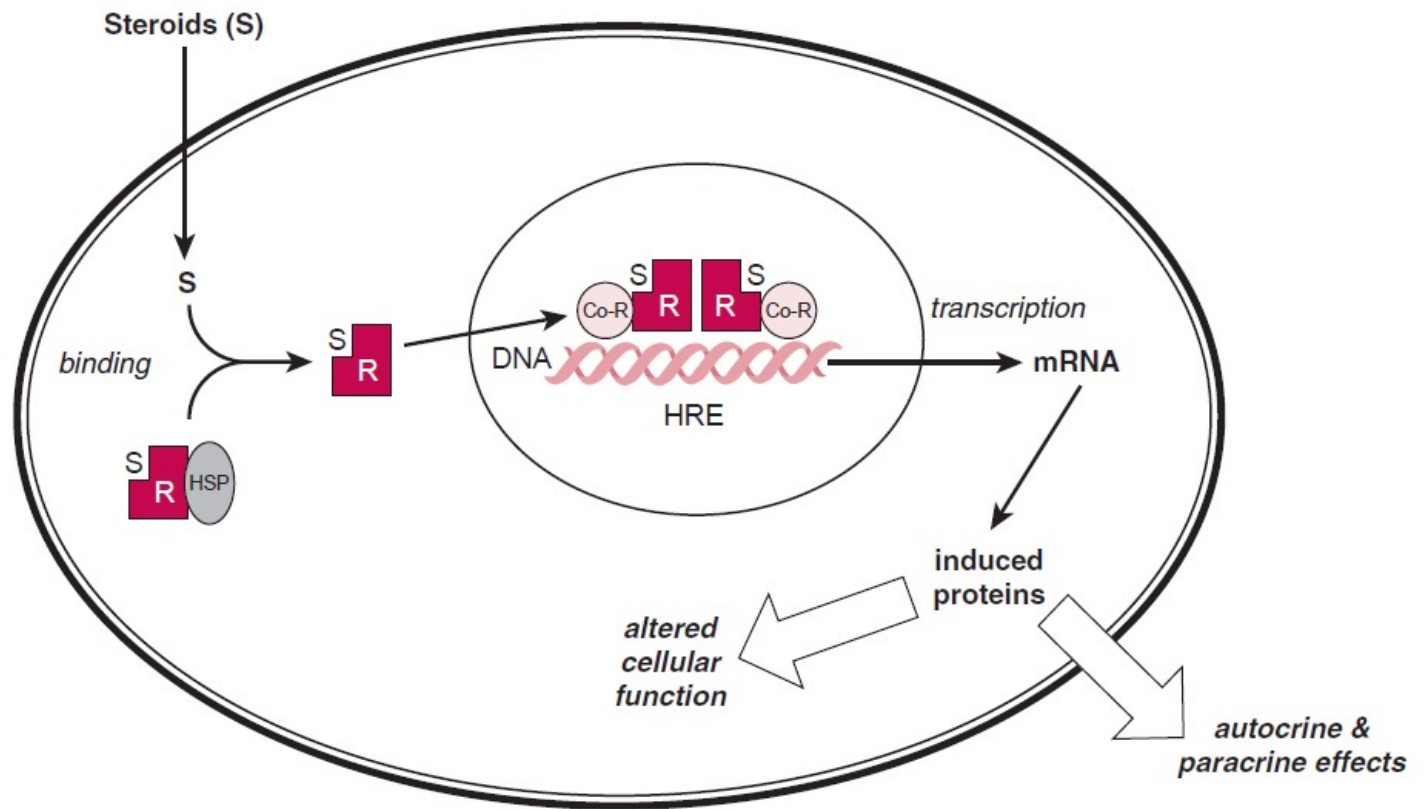
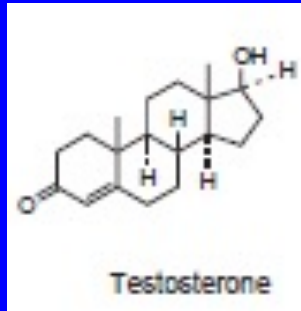
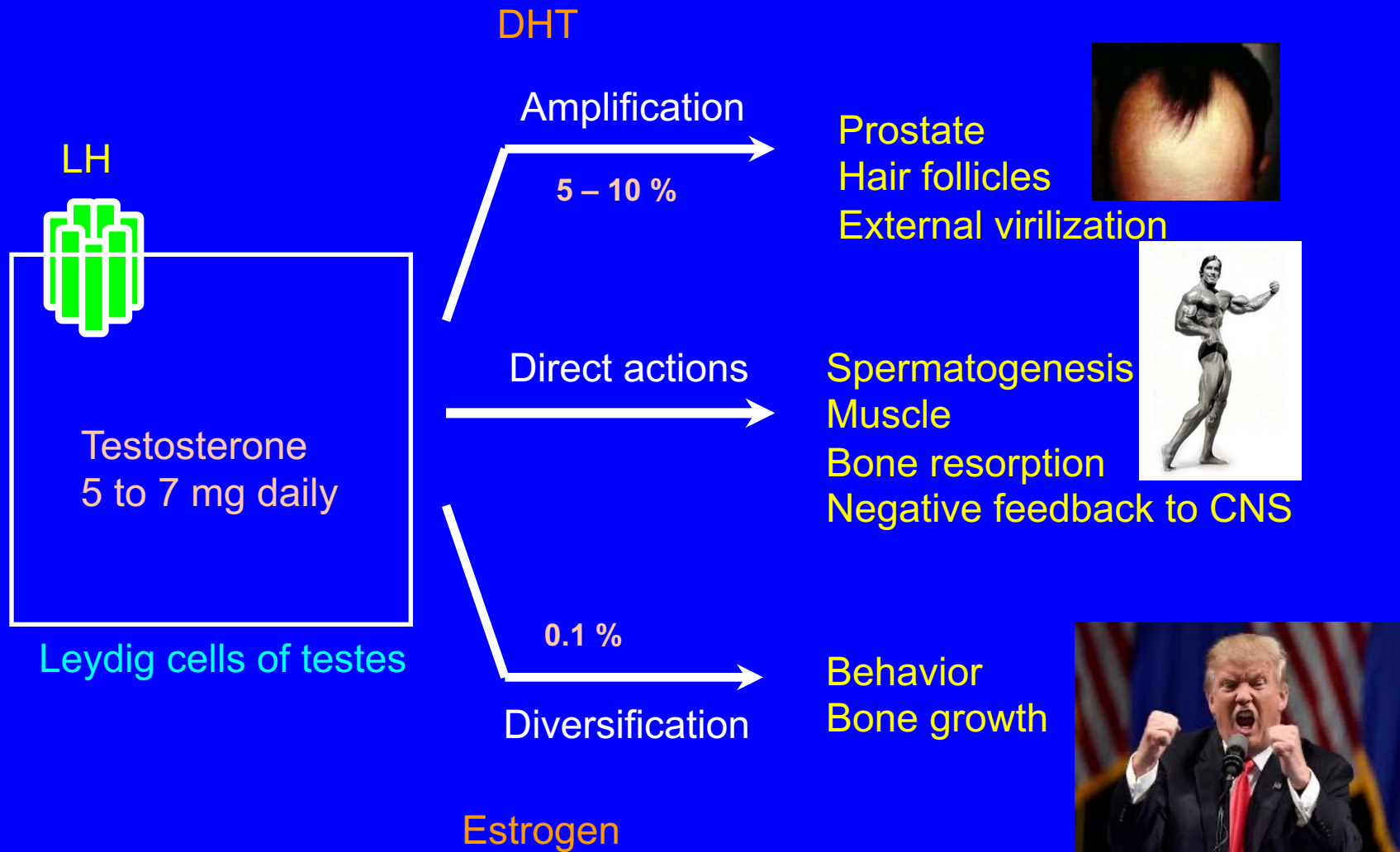
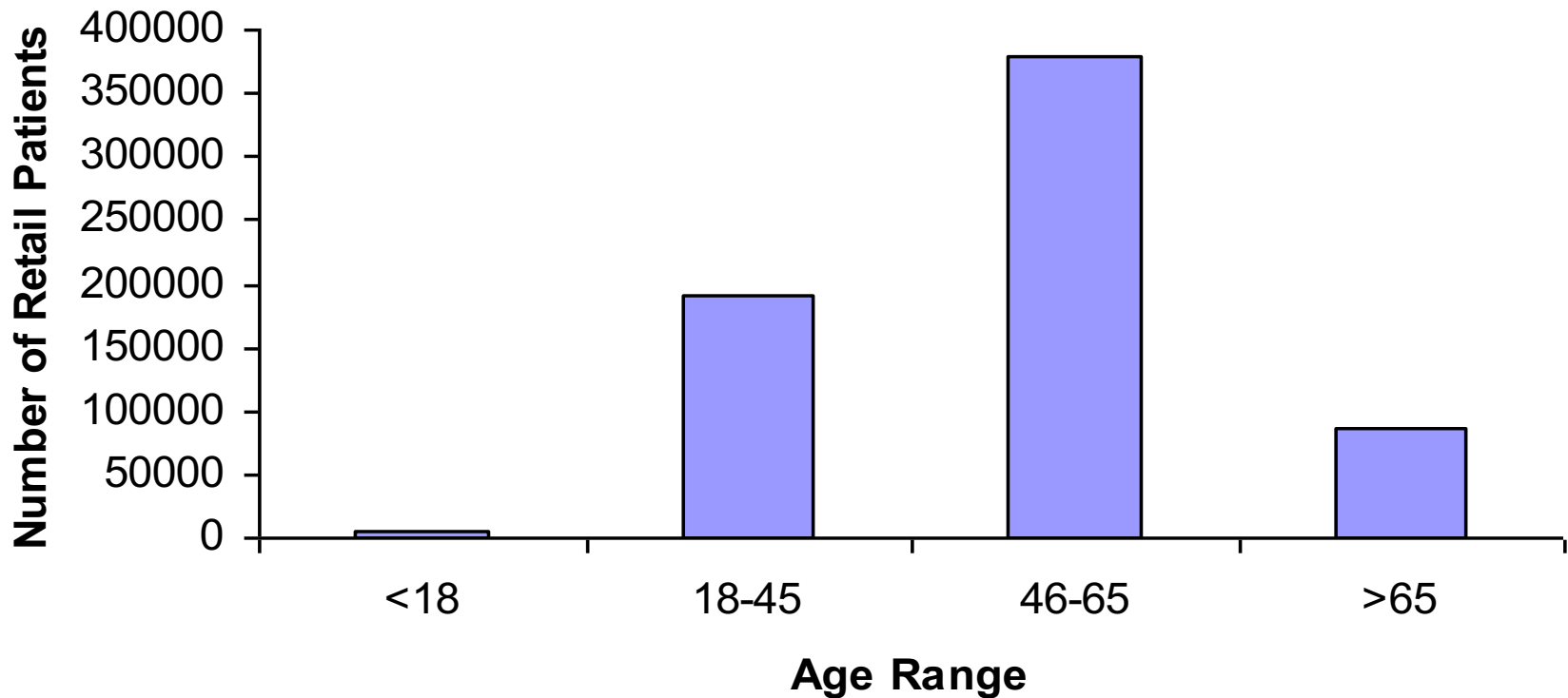


FIGURE 28.5 Mechanism of steroid hormone action.

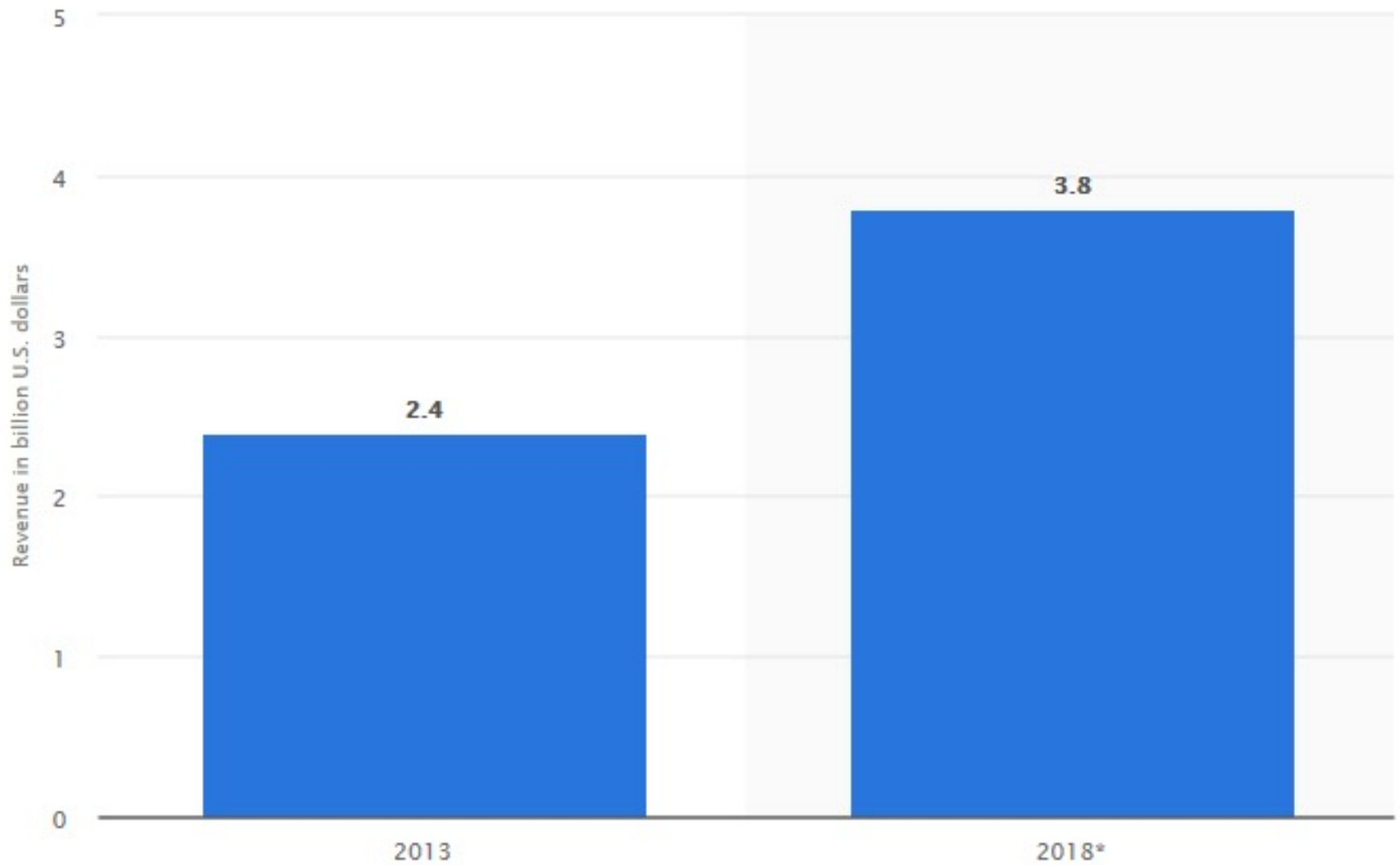
Androgen Physiology



Total Retail Patient Count in 2002



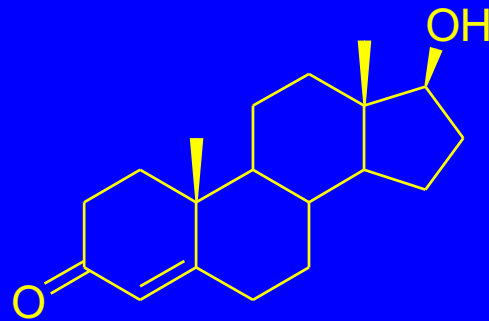
Testosterone and Aging Clinical Research Directions, Institute of Medicine (2004).



Testosterone Sales 2013, Projected 2018

Testosterone in HRT

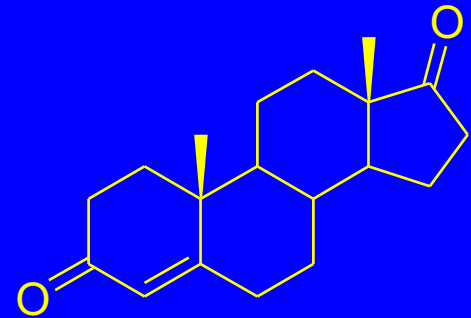
- Average life span for males is increasing
- 47 years average life time in 1900
- 79 years average life time in 2000
- 81 years average life time in 2017



Testosterone



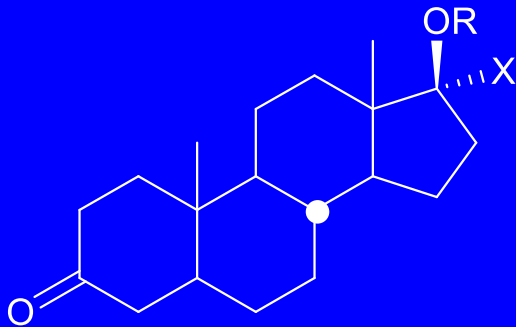
Tetrahydrogestrinone
THG



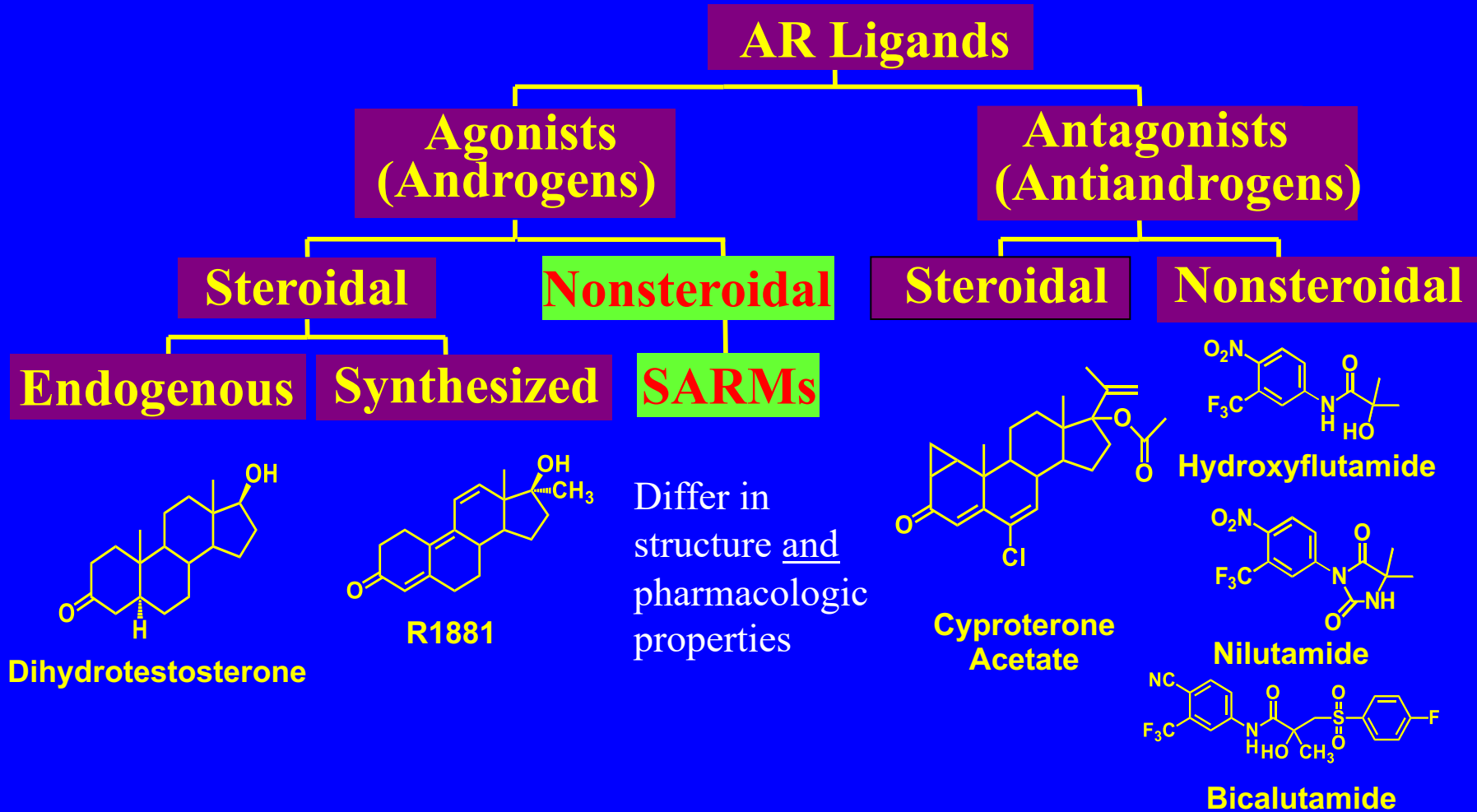
Androstenedione

Currently Available Testosterone Preparations

Oral	17- methyl testosterone Testosterone undecanoate (Andriol)
Parenteral	Injectable esters, ethanate, cypionate or propionate (Depo-Testosterone, Delatestryl, and generics)
Patches	Scrotal (Testoderm) Nonscrotal (Androderm)
Gels	Androgel, Testim, Axiron



Known AR Ligands (1997)



Risk/Benefit analysis of testosterone replacement

Benefits

- Increase libido & erectile function
- Increase fat-free muscle mass
- Decrease visceral fat
- Prevent osteoporosis
- Increase mood and cognition
- Increase hematocrit
- Increase strength
- Decrease fatigue

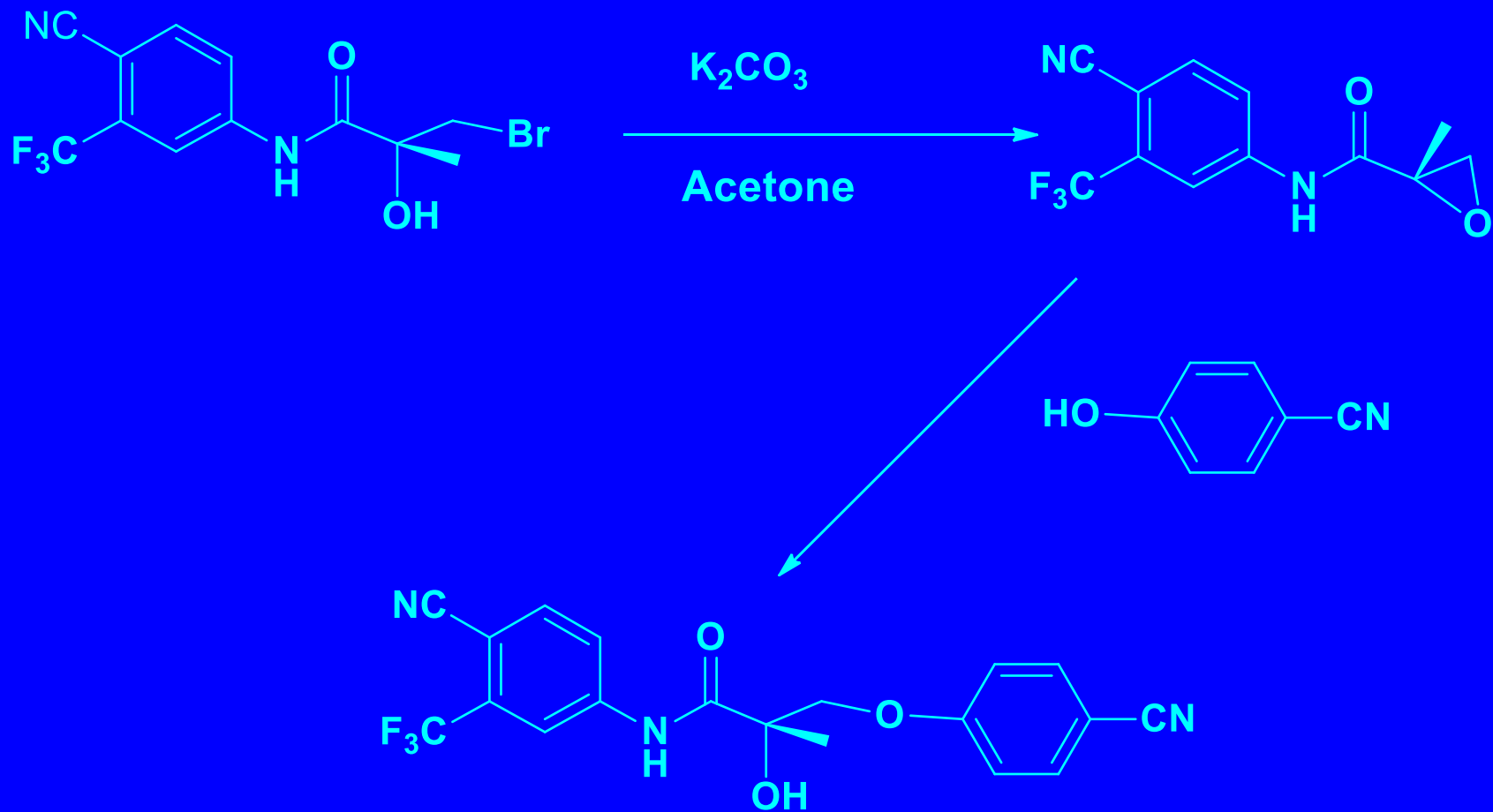
Risks

- Increase BPH and prostate cancer
- Unfavorable serum lipid profile
- CV complications
- Hepatotoxicity
- Gynecomastia
- Thrombogenicity
- Polycythemia
- Worsen sleep apnea

Ideal SARM

- Mimics the action of testosterone
- Avoids side effects of
 - Liver damage
 - Lipid changes
 - No endocrine actions (LH, FSH)
 - No prostate stimulation
- Orally active

General Synthetic Scheme

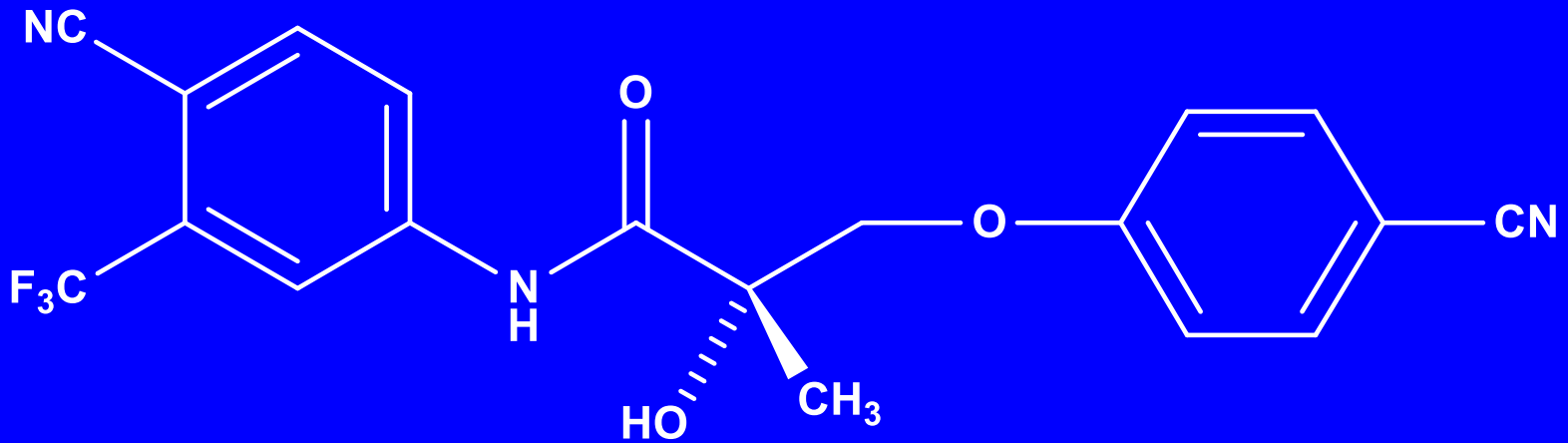


S-4

GTX-024

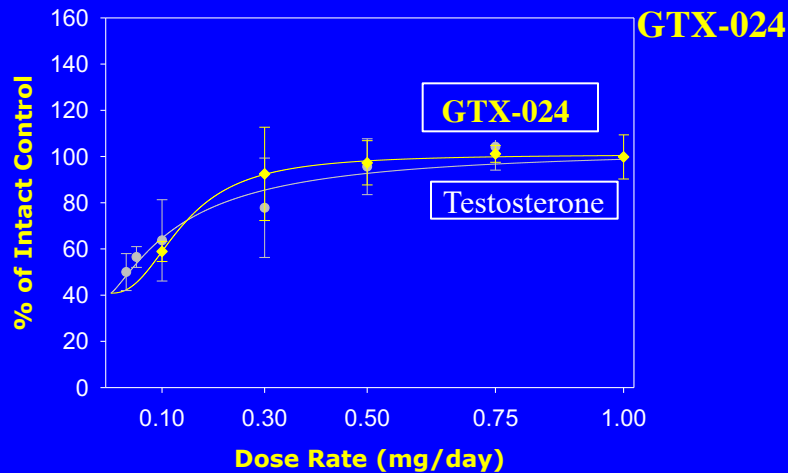
Ostarine

Enobosarm

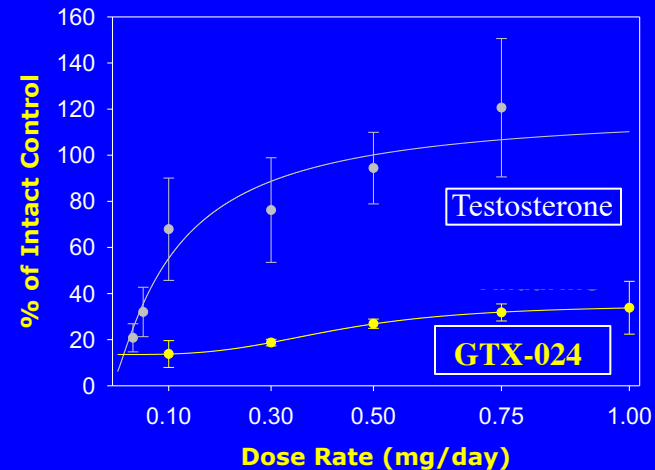


GTX-024 shows tissue-selective pharmacologic activity

Levator Ani muscle



Prostate

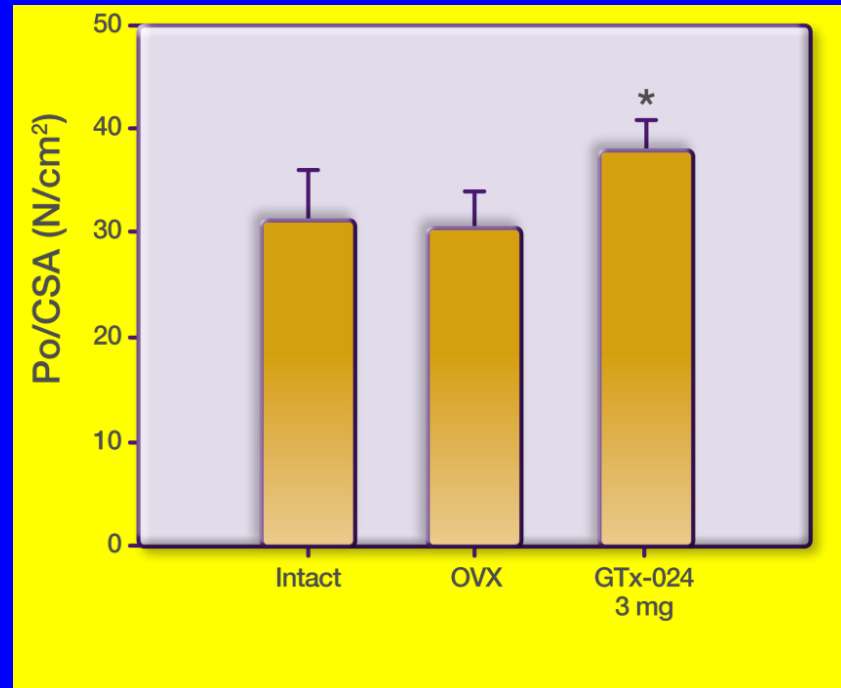


- GTX-024 is equipotent and efficacious to testosterone in levator ani muscle
- GTX-024 is a partial agonist in the prostate

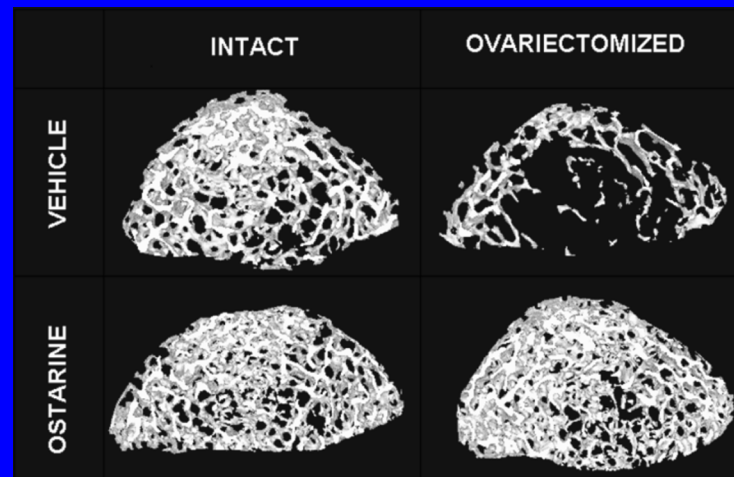


GTx-024 is anabolic in muscle and bone

- Female Sprague-Dawley rats divided into 3 groups
- Sham (vehicle), OVX (vehicle), OVX (GTx-024, 3 mg/d)
- Days 0-42: oral gavage with indicated treatment
- Day 42: Sacrifice. Soleus muscle dissected and used for strength analyses.



- Female Sprague-Dawley rats divided into 4 groups
- Sham (vehicle), OVX (vehicle), Sham and OVX (GTx-024, 3 mg/d)
- Days 0-42: oral gavage with indicated treatment
- Day 42: Sacrifice. Rat distal femur reconstructions (μ CT images from median animals in each group).



SARMs are specific for the androgen receptor

No cross-reactivity with:

- Estrogen receptor β
- Glucocorticoid receptor
- Mineralocorticoid receptor
- Progesterone receptor
- Estrogen receptor α
- Aromatase

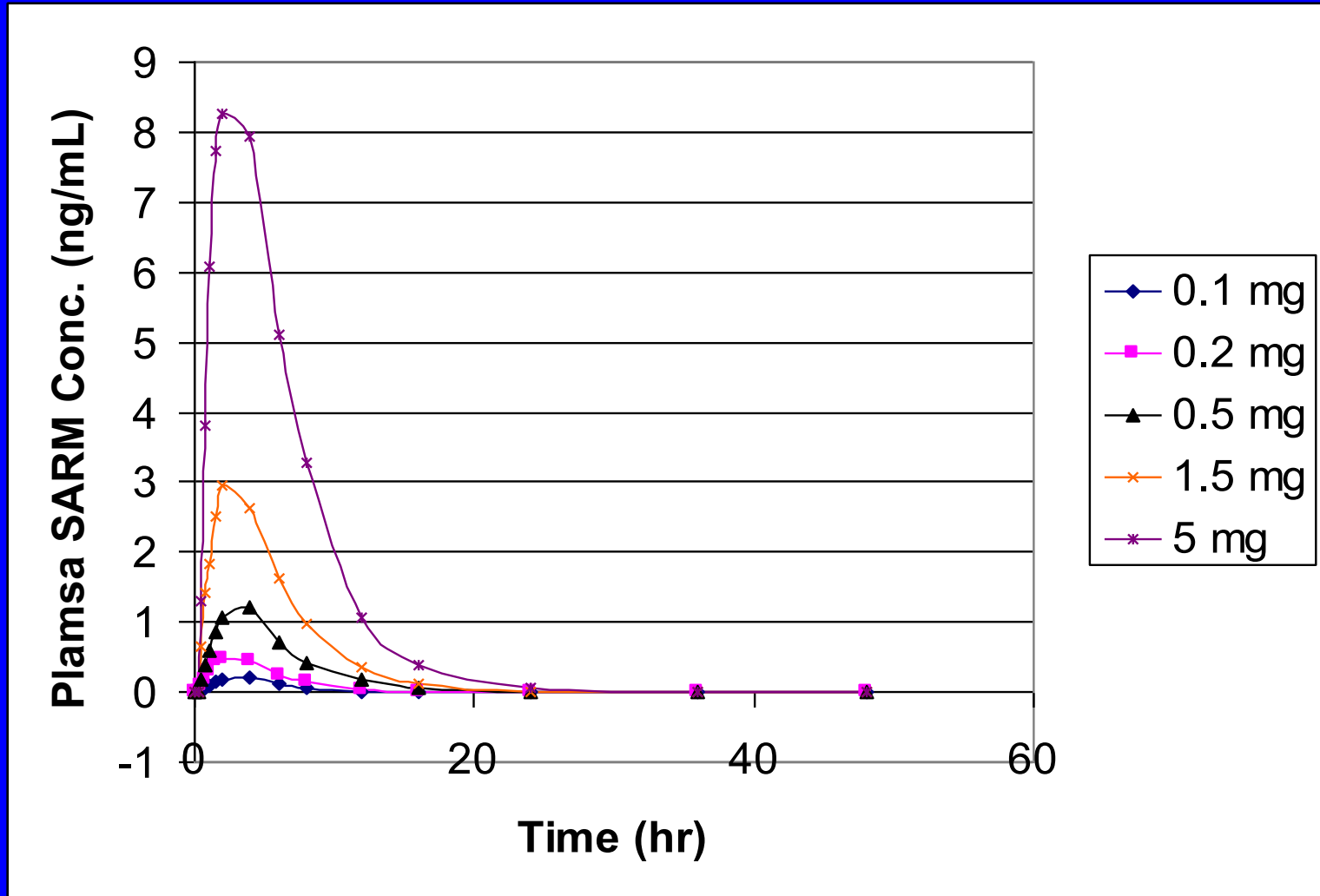
Interacts with:

- 5-Alpha reductase ($K_i = 100 \mu\text{M}$)
- Androgen receptor ($K_i = 7.94 \text{ nM}$)
- Serotonin Transporter ($K_i = 1.38 \mu\text{M}$)



This is the point where our laboratory turned the work over to clinical and started Phase 1 studies

GTX-024 is orally bioavailable and safe in humans



Enobosarm (GTX-024) consistently increased LBM and improved physical function

Phase IIb cancer cachexia trial:

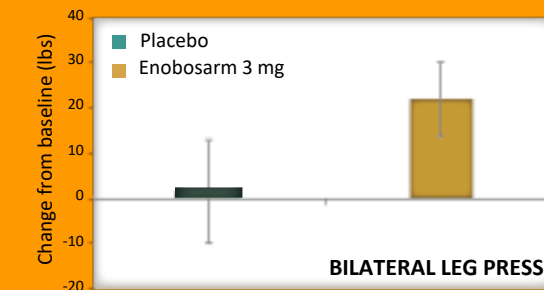
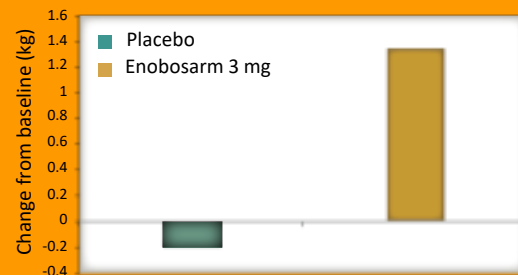
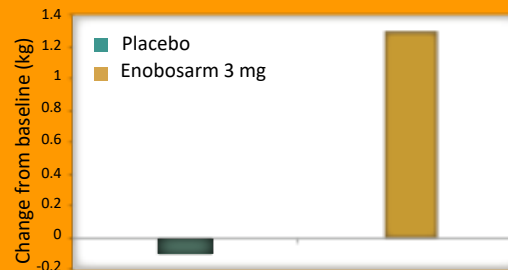
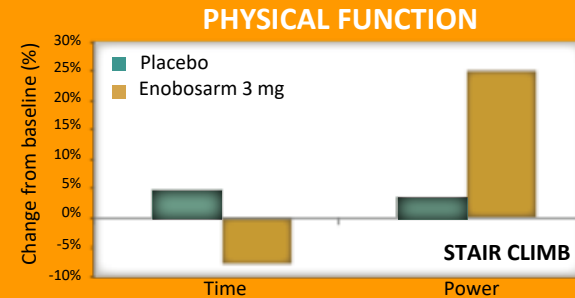
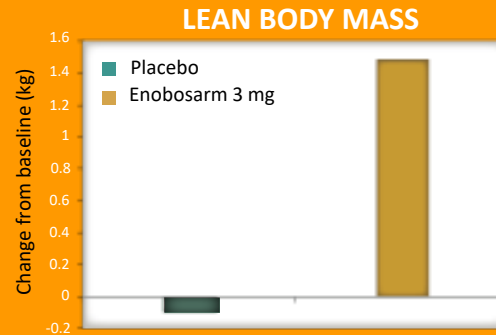
159 subjects with cancer cachexia,
4 months tx

Phase II POC clinical trial:

120 elderly men and postmenopausal women,
3 months tx

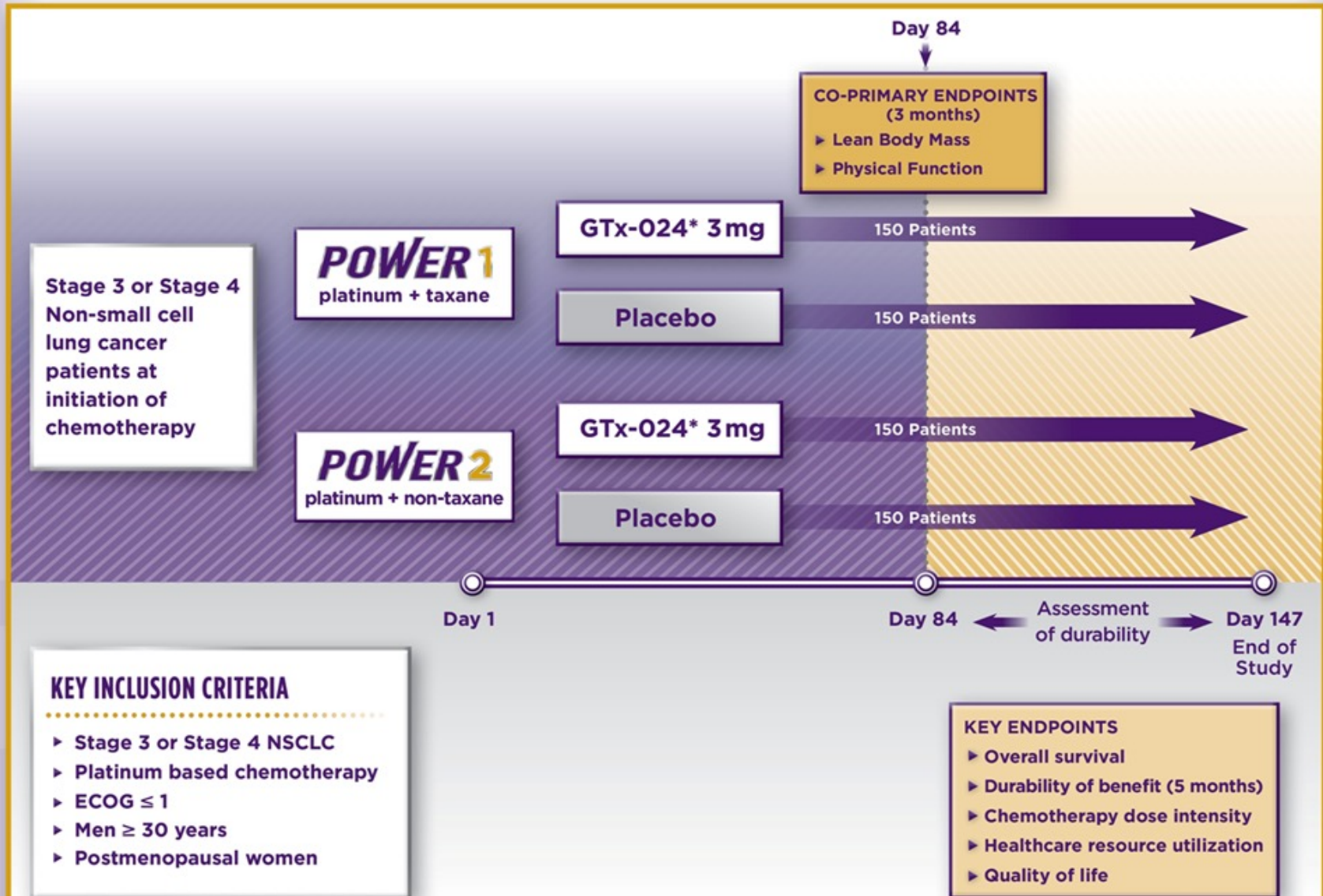
Phase Ib sarcopenia trial:

88 postmenopausal women, 3 months tx





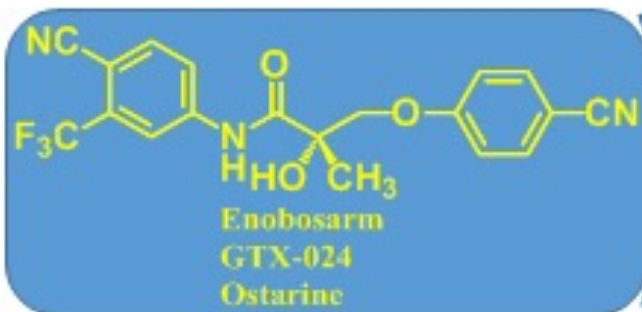
PREVENTION AND TREATMENT OF MUSCLE WASTING IN PATIENTS WITH CANCER



*GTx-024: once daily, oral selective androgen receptor modulator (SARM)

- Passed Phase I and II clinical trials in patients
- Not approved by the FDA in patients in phase III it increased muscle but was apparently not statistically effective enough for power ratings.





European Medicines
Agency (EMA)

2015
2016

U.S. Food and Drug
Administration

SARMs Patent Status

324 patent applications filed worldwide

144 applications filed in the US (provisional + utility)

54 issued US patents

Richard Magid, Ph.D.

Vice President

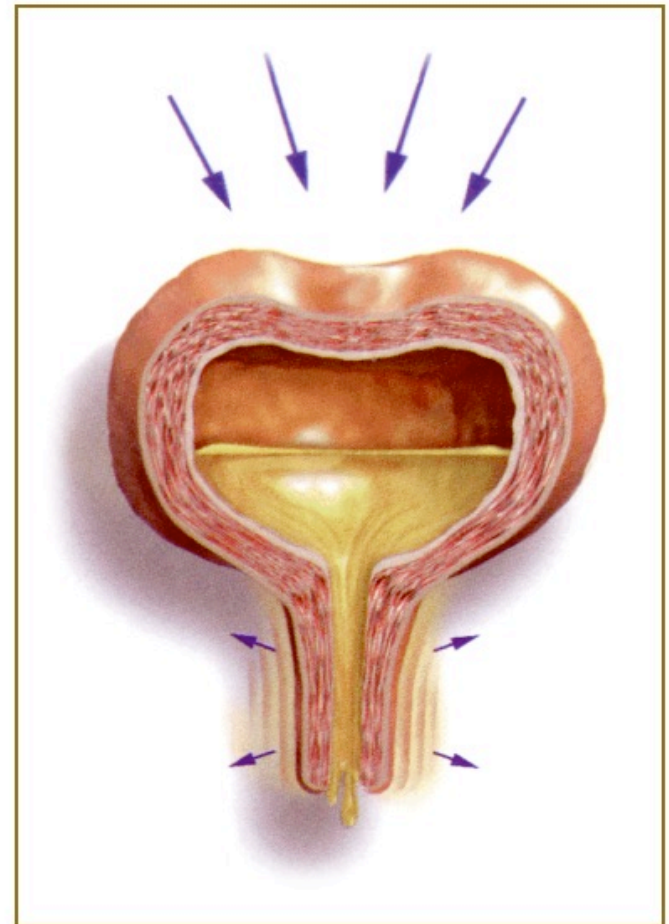
University of Tennessee Research Foundation

910 Madison Ave, Suite 827, Memphis, TN 38163

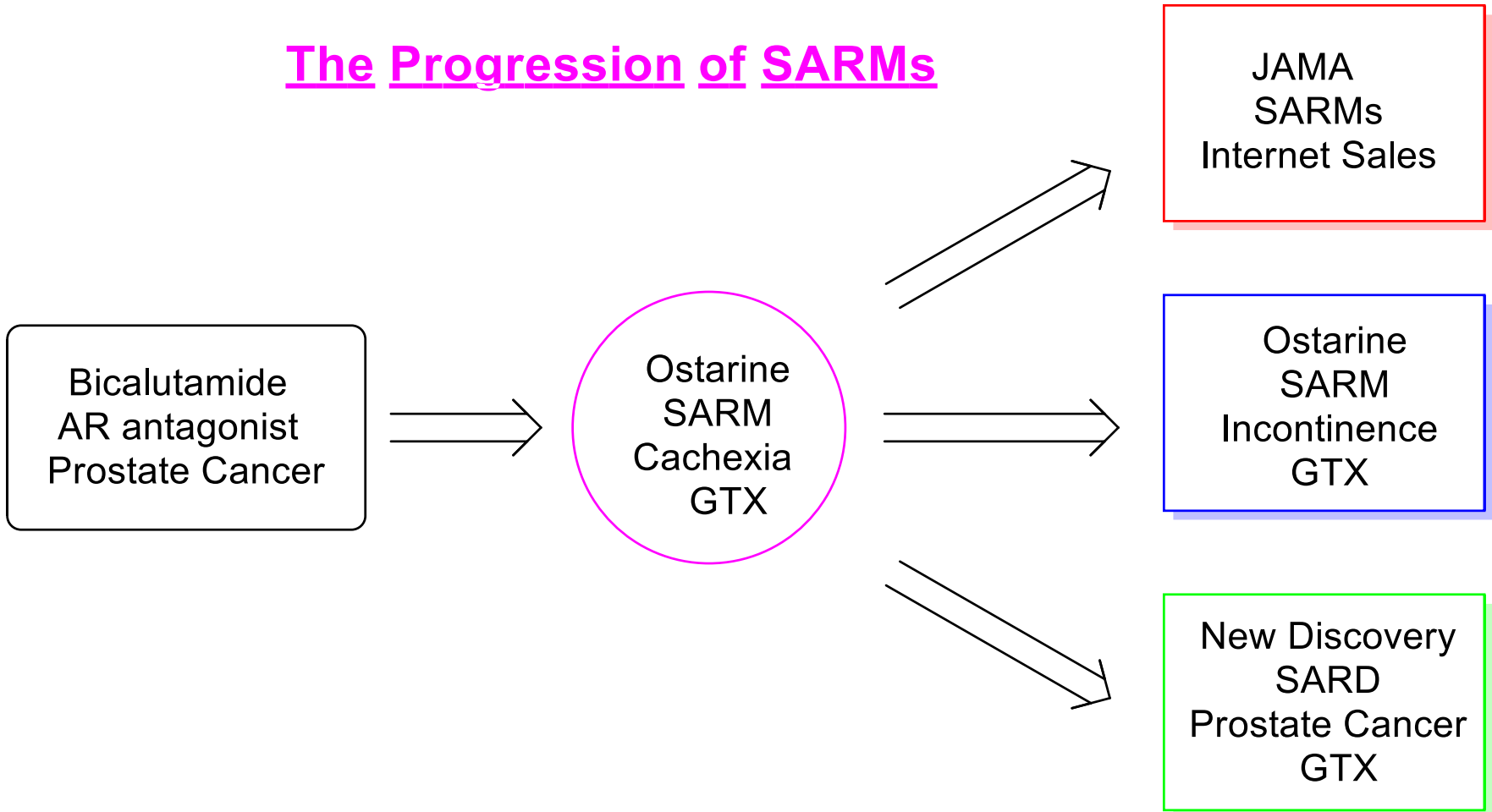
Light

Stress Urinary Incontinence *Sphincteric Incontinence*

- Symptom
 - Urine leakage during physical activity/exertion
- Sign
 - Visual proof of urine loss
- Condition
 - Weakened pelvic floor muscles
 - Exacerbated by pregnancy, childbirth and menopause
 - Different than urge incontinence



The Progression of SARMs



Problem ??

Internet Sales

Dismayed and Frustrated xx

I Don't Know What to Do \$\$\$\$

I will share my major concern in one specific area

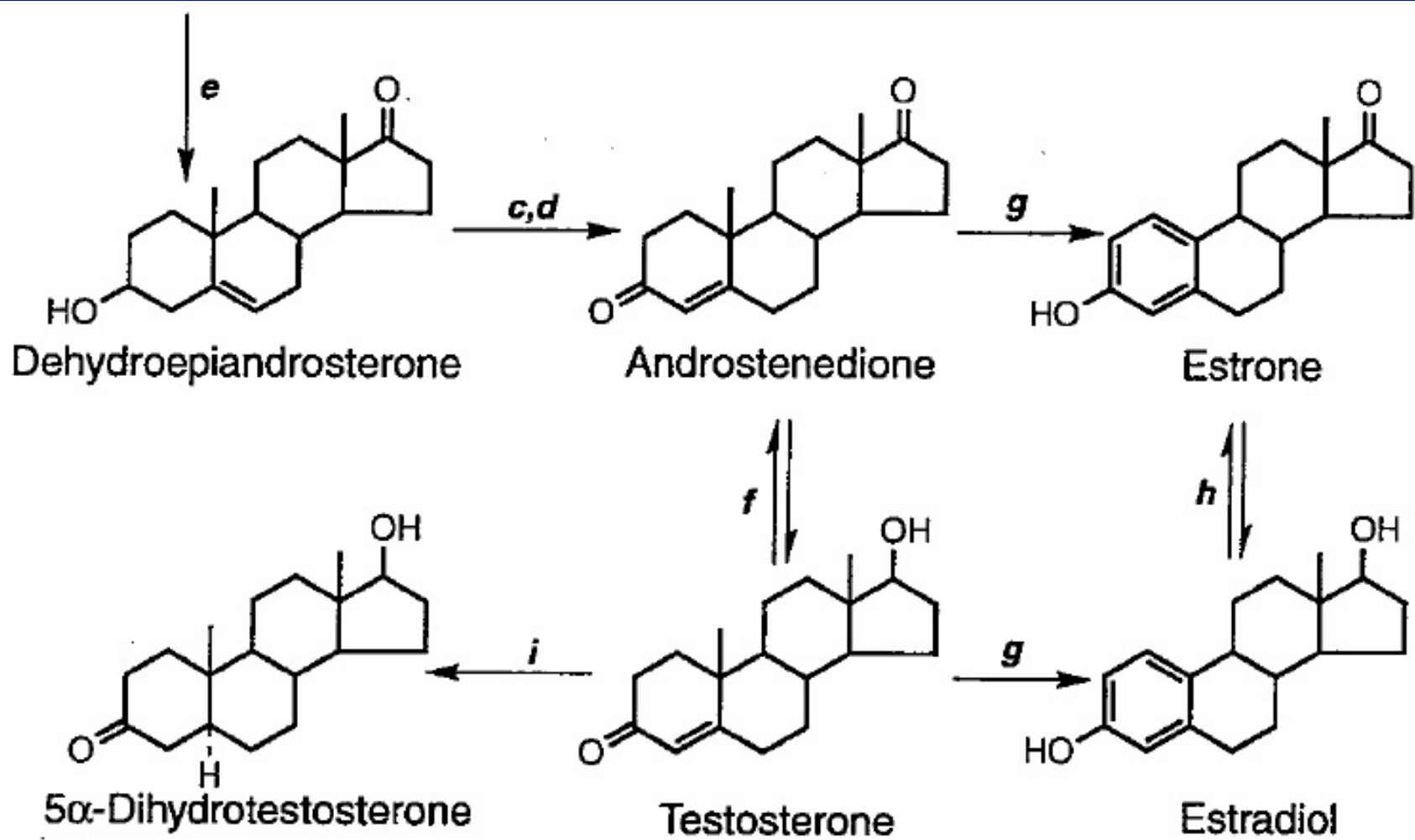
**I would like to hear a possible
solution !!!!**

Wall Street Journal , October 12, 2017



Anthony Hughes, known as Dr. Huge, promotes SARMs in a series of YouTube videos. PHOTO: VIR FX MEDIA

In the world of bodybuilding, a former bankruptcy lawyer has gained a following as a YouTube personality nicknamed Dr. Huge, whose videos extol an experimental line of drugs he promotes as a safer alternative to steroids.



A couple of years ago, Mr. Hughes wound down his legal practice as he embarked on a new career as “Dr. Huge,” hopscotching the globe promoting SARMs and networking at bodybuilding events.

While clinical trials are pending, the FDA has warned at least one online vendor that SARMs are drugs subject to strict regulation and “present significant potential safety risks.” Selling them without the agency’s approval is unlawful, the FDA says.

But the FDA hasn’t made a priority of cracking down on SARMs sales. Federal officials say such a move requires significant resources.

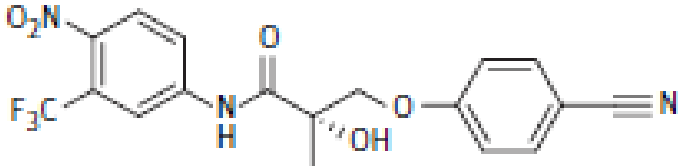
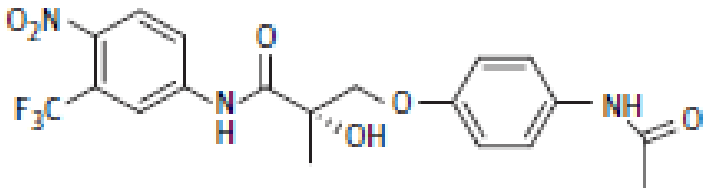
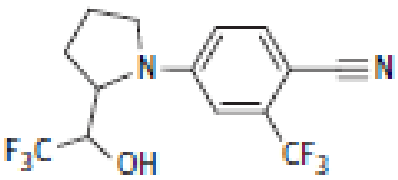
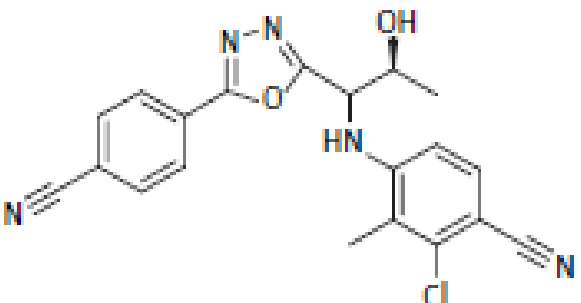
Wall Street Journal , October 12, 2017

“I wish [the FDA] would do more” to police the market, said Duane D. Miller, a University of Tennessee chemist who was part of the team that developed SARMs in the late 1990s. The university later patented and licensed research that Prof. Miller says is being exploited by online vendors.

Wall Street Journal , October 12, 2017



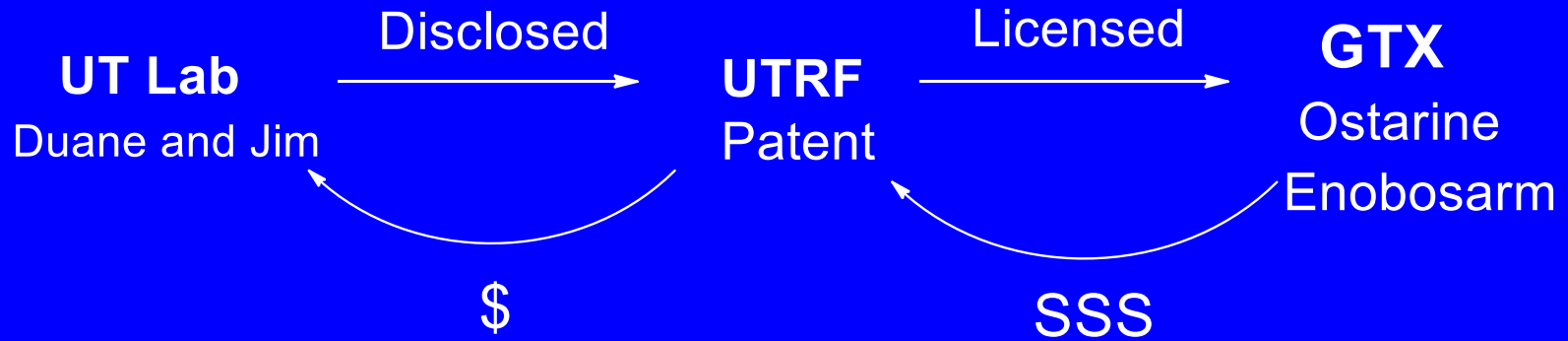
Figure 2. Pharmacological Classes of Appearance and Performance Enhancing Substances Found in the Search

Compound	Chemical Structure	Modes of Action	Synonyms
Ostarine		SARM	Enobosarm ^a ; GTx-024; MK-2866; S-22; S22; (2S)-3-(4-cyanophenoxy)-N-(4-cyano-3-trifluoromethylphenyl)-2-hydroxy-2-methylpropanamide
Andarine		SARM	Andarine ^a ; GTx-007
LGD-4033		SARM	Ligandrol ^a ; 4-((R)-2-((R)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl)-2-trifluoromethylbenzonitrile
RAD140		SARM	Testolone ^a ; 2-chloro-4-((1R,2S)-1-(5-(4-cyanophenyl)-1,3,4-oxadiazol-2-yl)-2-hydroxypropylamino)-3-methylbenzonitrile

Chemical Composition and Labeling of Substances Marketed as Selective Androgen Receptor Modulators and Sold via the Internet

RESULTS Among 44 products marketed and sold as selective androgen receptor modulators, only 23 (52%) contained 1 or more selective androgen receptor modulators (Ostarine, LGD-4033, or Andarine).

Entrepreneurship



Unauthorized Use





Richard Magid, Ph.D.

UTRF Vice President



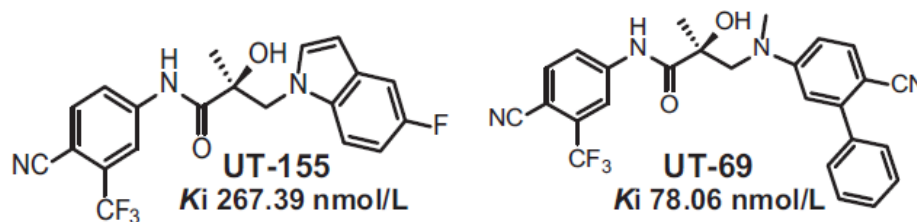
Stefan Schweizer, Ph.D., M.B.A.

Licensing Associate, Health Science Center

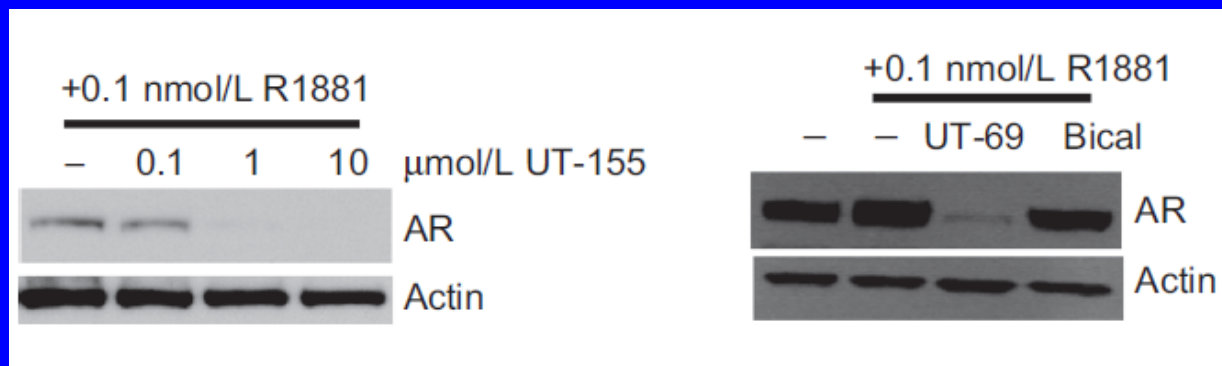
Novel Selective Agents for the Degradation of Androgen Receptor Variants to Treat Castration-Resistant Prostate Cancer



Suriyan Ponnusamy¹, Christopher C. Coss², Thirumagal Thiyagarajan¹, Kate Watts³, Dong-Jin Hwang⁴, Yali He⁴, Luke A. Selth^{5,6}, Iain J. McEwan³, Charles B. Duke⁴, Jayaprakash Pagadala⁴, Geetika Singh⁷, Robert W. Wake⁸, Christopher Ledbetter⁸, Wayne D. Tilley^{5,6}, Tudor Moldoveanu⁷, James T. Dalton², Duane D. Miller⁴, and Ramesh Narayanan^{1,9}



C





FUTURE

Dark

Internet Unauthorized Sale Enobosarm (Ostarine)

Light

Phase II Trial Postmenopausal Women Incontinence
Stress Urinary Incontinence (SUI)

HOPE

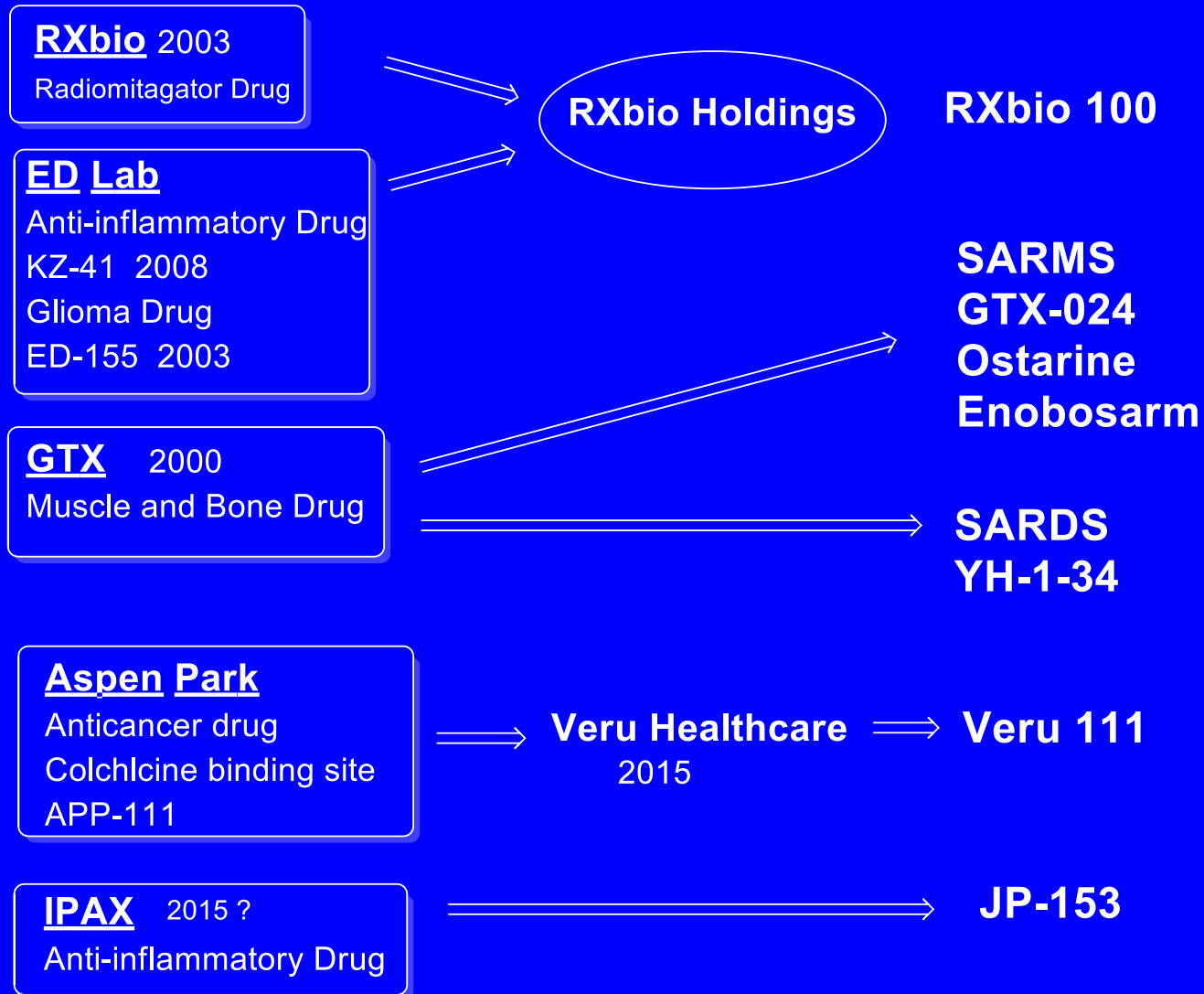
YH-1-34 SARs

Treat Resistant Enzalutamide Prostate Cancer

Discovered Drugs in Our UTHSC Laboratory



UTRF licensed to start up companies





Aspen Park

Anticancer drug

Colchicine binding site

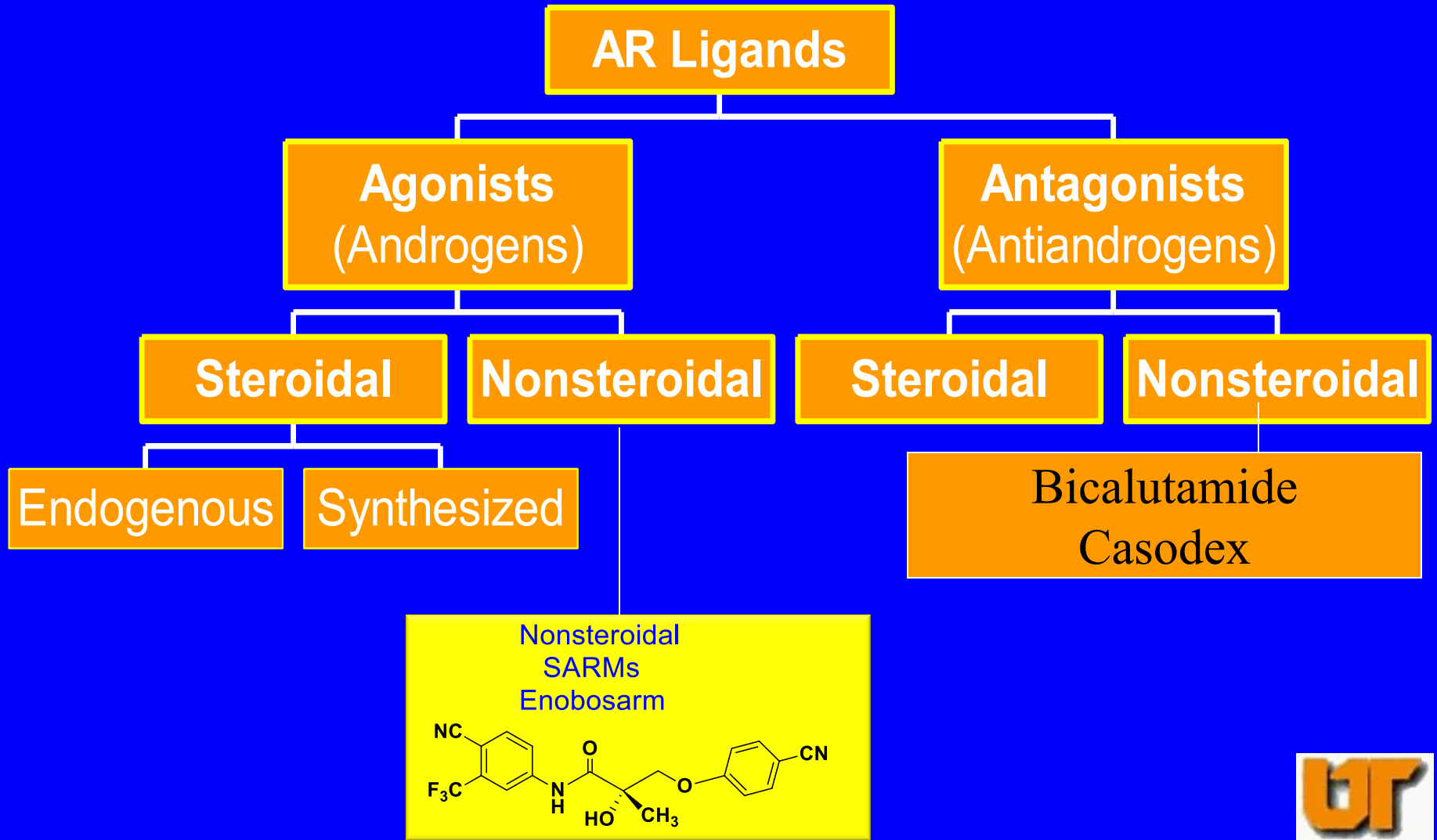
APP-111

⇒ **Veru Healthcare** ⇒ **Veru 111**

Summary

- Discovered nonsteroidal SARMs
- Identified tissue selective SARMs
- Bright future for SARM therapy
- 324 SARM patents in Progress
 - 52 US patents
 - Enobosarm (GTX-024) in Phase II clinical

Androgen Receptor (AR) Ligands



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“Happiness dies when it is not shared”

Quote by Will Durant