“From Androgen Receptor Ligand Discovery to Potential Therapeutic Uses”

Duane D. Miller, Ph.D.
Department of Pharmaceutical Sciences
University of Tennessee
Thanks
Sarah Ashley Block, Director | Office of Research Communications & Marketing

Department of Pharmaceutical Sciences (Staff)
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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

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.
Design

Drug Design → Synthesis Analytics → Molecular Pharm. → Preclinical → Clinical Phases I, II, III → FDA review → FDA Approval

Development

NIH, DOD → UTRF → External Companies

Veru
RxBio Inc
EDLabs
Molecular Design International
Testosterone Levels Relative To Age

AGE 35 40 45 50 55 60 65 70 75 80 85

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

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

- **Testosterone**
  - 5 to 7 mg daily
  - Amplification: 5 – 10%
  - Direct actions: Spermatogenesis, Muscle, Bone resorption, Negative feedback to CNS
  - Diversification: DHT, Prostate, Hair follicles, External virilization
  - Estrogen: Behavior, Bone growth
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
Tetrahydrogestrinone (THG)

Testosterone

Androstendione
Currently Available Testosterone Preparations

**Oral**
- 17- methyl testosterone
- Testosterone undecanote (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)

AR Ligands
- **Agonists (Androgens)**
  - Steroidal
  - Nonsteroidal
- **Antagonists (Antiandrogens)**
  - Steroidal
  - Nonsteroidal

**Steroidal**
- **Endogenous**
  - Dihydrotestosterone
- **Synthesized**
  - R1881

**Nonsteroidal**
- **SARMs**

**Differ in structure and pharmacologic properties**

Endogenous:
- Dihydrotestosterone
- R1881

Synthesized:
- Cyproterone Acetate
- Hydroxyflutamide
- Nilutamide
- Bicalutamide
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

\[
\begin{align*}
\text{NC} & \quad \text{OH} \\
F_3C & \quad \text{Br} \\
\text{HO} & \quad \text{CN}
\end{align*}
\]
S-4
GTX-024
Ostarine
Enobosarm
GTX-024 shows tissue-selective pharmacologic activity

- 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 (μCT 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 (Ki = 100 µM)
- Androgen receptor (Ki = 7.94 nM)
- Serotonin Transporter (Ki = 1.38 µM)
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

**POWER**

Prevention and Treatment of Muscle Wasting in Patients with Cancer

**POWER1**
- Stage 3 or Stage 4
- Non-small cell lung cancer
- Patients at initiation of chemotherapy
- Platinum + Taxane
- 3 mg GTx-024
- 150 Patients

**POWER2**
- Platinum + Non-taxane
- 3 mg GTx-024
- 150 Patients

**Placebo**
- 150 Patients

**CO-PRIMARY ENDPOINTS**
- Lean Body Mass
- Physical Function

**Day 1**

**Day 84**
- Assessment of durability

**Day 147**
- End of Study

**KEY INCLUSION CRITERIA**
- Stage 3 or Stage 4 NSCLC
- Platinum based chemotherapy
- ECOG ≤ 1
- Men ≥ 30 years
- Postmenopausal women

**KEY ENDPOINTS**
- Overall survival
- Durability of benefit (5 months)
- Chemotherapy dose intensity
- Healthcare resource utilization
- Quality of life

*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.
**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
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

- Bicalutamide
  - AR antagonist
  - Prostate Cancer

- Ostarine
  - SARM
  - Cachexia
  - GTX

- JAMA
  - SARMs
  - Internet Sales

- Ostarine
  - SARM
  - Incontinence
  - GTX

- New Discovery
  - SARD
  - Prostate Cancer
  - GTX
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 !!!!
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
<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical Structure</th>
<th>Modes of Action</th>
<th>Synonyms</th>
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<tbody>
<tr>
<td>Ostarine</td>
<td><img src="image" alt="Ostarine Chemical Structure" /></td>
<td>SARM</td>
<td>Enobosarm; GTx-024; MK-2866; S-22; S22; (25)-3-(4-cyanophenoxy)-N-(4-cyano-3-trifluoromethyl(phenyl)-2-hydroxy-2-methylpropanamide</td>
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<tr>
<td>Andarine</td>
<td><img src="image" alt="Andarine Chemical Structure" /></td>
<td>SARM</td>
<td>Andarine; GTx-007</td>
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<tr>
<td>LGD-4033</td>
<td><img src="image" alt="LGD-4033 Chemical Structure" /></td>
<td>SARM</td>
<td>Ligandrol; 4-((R)-2-((R)-2,2,2-trifluoro-1-hydroxyethyl)pyrrolidin-1-yl))-2-trifluoromethylbenzonitrile</td>
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<tr>
<td>RAD140</td>
<td><img src="image" alt="RAD140 Chemical Structure" /></td>
<td>SARM</td>
<td>Testolone; 2-chloro-4-((1R,2S)-1-(5-(4-cyanophenyl)-1,3,4-oxadiazol-2-yl)-2-hydroxypropylamino)-3-methylbenzonitrile</td>
</tr>
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</table>
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).
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. Selth⁵,⁶ Iain J. McEwan³, Charles B. Duke⁴, Jayaprakash Pagadala⁴, Geetika Singh⁷, Robert W. Wake⁸, Christopher Ledbetter⁸, Wayne D. Tilley⁵,⁶, Tudor Moldoveanu⁷, James T. Dalton², Duane D. Miller⁴, and Ramesh Narayanan¹,⁹
FUTURE

Dark
Internet Unauthorized Sale Enobosarm (Ostarine)

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

HOPE
YH-1-34 SARDs
Treat Resistant Enzalutamide Prostate Cancer
Discovered Drugs in Our UTHSC Laboratory

UTRF licensed to start up companies

**RXbio** 2003
Radiomitagator Drug

**ED Lab**
Anti-inflammatory Drug
KZ-41 2008
Glioma Drug
ED-155 2003

**GTX** 2000
Muscle and Bone Drug

**Aspen Park**
Anticancer drug
Colchicine binding site
APP-111

**IPAX** 2015?
Anti-inflammatory Drug

**RXbio Holdings**

**RXbio 100**
SARMS
GTX-024
Ostarine
Enobosarm

**SARDS**
YH-1-34

**Veru Healthcare**
Veru 111
2015

**JP-153**
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

- Agonists (Androgens)
  - Steroidal
  - Nonsteroidal
- Antagonists (Antiandrogens)
  - Steroidal
  - Nonsteroidal

Endogenous Synthesized

- Bicalutamide
- Casodex

Nonsteroidal SARMs
- Enobosarm
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GTx, Inc.
“Happiness dies when it is not shared”

Quote by Will Durant