Androgens and Selective Androgen Receptor Modulators

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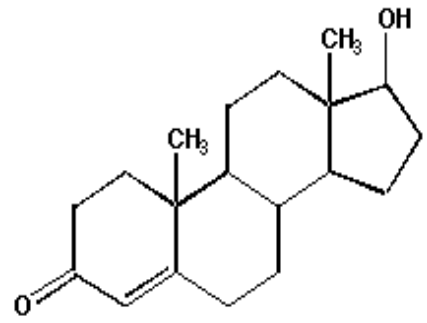

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- Consultation: AbbVie, OPKO
- Equity interest/stock: FPT, LLC
- Patents: Free Testosterone Algorithm; Selective Testosterone Therapy
- Not speaking to represent:
  - ABIM Endocrinology Board
  - Endocrine Society

Selective Androgen Receptor Modulators

- SARMs are ligands that bind AR and induce tissue-specific transcriptional activation of AR-dependent genes
  - Dual anabolics on muscle and bone and reduce adiposity
- Two function classes: AR Agonist; AR Antagonist
- Two structural classes: steroidal and nonsteroidal
- Mechanisms of tissue selectivity:
  - Conformational hypothesis
  - Co-activator hypothesis: altered co-activator and N-terminal interaction profile
  - 5-α reductase hypothesis

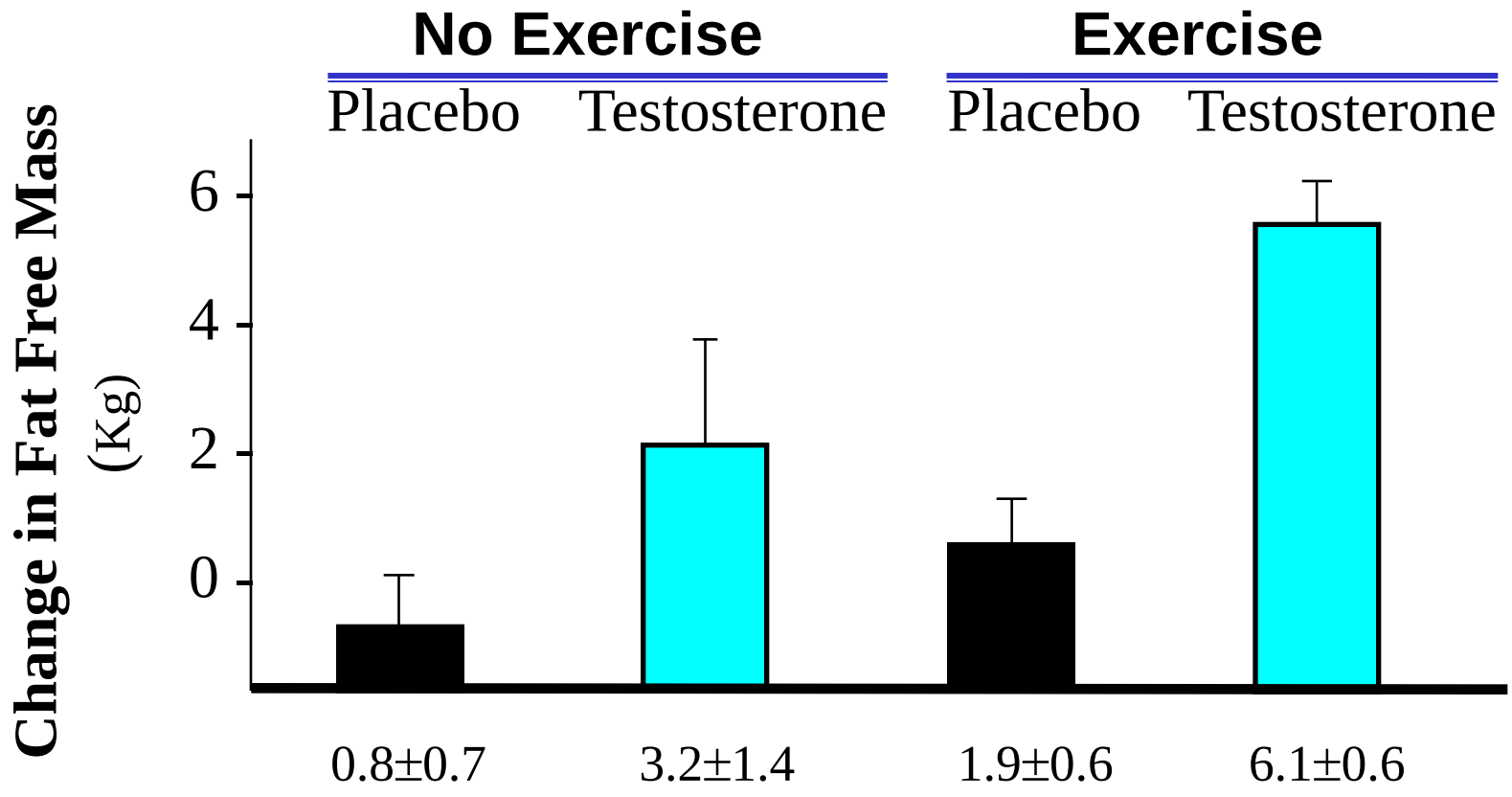
Bhasin S et al. *Nature Endocrinol Metab* 2006;2:146.

Indications Other than Hypogonadism for which Androgens/ SARMs are being Investigated

- Mobility Disorders, Sarcopenia, and Cachexia Associated with Aging and Chronic Diseases
- Anemias
- Osteoporosis
- Fatigue
- Late-onset low grade progressive depressive disorder (dysthymia)
- Muscular dystrophies
- Angioneurotic edema
- Preventing progression to dementia in preclinical AD
- Autoimmune disorders

Bhasin S et al. *Nature Endocrinol Metab* 2006;2:146.

Effects of A Supraphysiologic Dose of Testosterone on Fat–Free Mass in Healthy Men



Bhasin et al, *N Engl J Med* 1996;335:1-7

Major RCTs of Testosterone's Effects in Older Adults

Trial	Eligibility	Baseline T	Symptom Requirement	Outcomes
TTrials – Physical Function Trial (n=780), 1 year	≥65 years	Average of two T levels < 275 ng/dL	Mobility difficulty, 6MWS <1.2 m/sec	6MWD, PF10, and PGIC FACIT-1
TEAAM Trial (n=308); 3 years	≥60 years	TT < 400 ng/dL and/or free T <50 pg/mL	No symptom requirement	Muscle mass, strength and power, physical function, self-reported function
TOM Trial (n=209); 6 months	65 years or older	TT <350 ng/dL and/ or free T <50 pg/mL	Self-reported mobility difficulty, SPPB 4 to 9	LBM, strength and power, loaded and unloaded gait speed and stair climbing power, fatigue, disability, PGIC
Wu et al (n= 274); 6 months	Men, 65 years or older	TT <340 ng/L, or free T <83 pg/mL	Frail and intermediate frail	LBM, strength, muscle strength, physical function, and self-reported quality of life
Emmelot-Wonk Trial (n=237); 6 months	60 to 80 years	TT <400 ng/dL	No symptom requirement	LBM, strength, TUG, self-reported functional mobility
Nair et al (n=58); 2 years	60 or older	Bio-T < 103 ng/dL	No symptom requirement	LBM, strength, VO2max, BMD

Snyder et al, NEJM 2016;374:611-24; Basaria et al, JAMA 2015;314:570-81; Basaria et al, NEJM 2010;363:109-22.; Srinivas Shankar et al, JCEM 2010;95:639-50; Emmelot-Wonk et al, JAMA 2008;299:39-52; Nair et al, NEJM 2006;355:1647.

RCT Data on Testosterone's Effects on Muscle Mass, Muscle Performance and Physical Function

- Testosterone administration increases:
  - Skeletal muscle mass,
  - Maximal voluntary strength and muscle power,
  - VO_{2peak}
  - Self-reported function
  - Stair climbing speed and power; and walking ability
- The anabolic effects of testosterone on muscle mass and strength are augmented by resistance exercise training and rhGH, but not by protein supplementation.
- These anabolic effects on muscle mass and strength measures have been demonstrated in healthy men, hypogonadal men, community-dwelling older men, older men with mobility limitation, men with chronic disease (HIV-infected men with weight loss, COPD, ESRD).

Snyder et al, NEJM 2016;374:611-24; Basaria et al, JAMA 2015;314:570-81; Basaria et al, NEJM 2010;363:109-22; Srinivas Shankar et al, JCEM 2010;95:639-50; Emmelot-Wonk et al, JAMA 2008;299:39-52; Nair et al, NEJM 2006;355:1647.

Effects on Other Endpoints

Endpoint	Findings of RCTs
Bone	Improvements in vBMD, aBMD, and estimated bone strength of hip and spine
Anemia	Corrected unexplained anemia of aging and anemia of other causes
Depressive symptoms	Small improvements in depressive symptoms; some efficacy in late-onset PDD
HRQOL	Improves physical function domain score
Fatigue	No improvement
Cognition	No improvement in cognition community-dwelling men; Efficacy in men with preclinical AD?
Safety	Erythrocytosis most frequent AE; no trial large enough or long enough for MACE and prostate events

TRAVERSE Trial: Cardiovascular safety trial in 6,000 middle aged and older men at increased MACE risk treated with placebo or T for up to 5 years

Basaria et al, NEJM 2010; Bhasin et al, JAMA Psych 2018; Snyder et al, JAMA IM 2017; Basaria et al, JAMA 2015; Huang et al, Lancet Diabetes Endocrinol 2016; Resnick et al, JAMA 2017; Travison et al, J Gerontol 2011

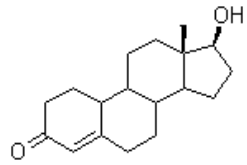
Lessons Learned from Testosterone RCTs

- Triple acting drugs: dual anabolic on muscle and bone, reduce adiposity
- Testosterone's anabolic effects on muscle mass and strength are dose-related: with supraphysiologic doses, very substantial gains in muscle mass and muscle strength are achievable in young and older men.
- Concerns about potential adverse effects have limited the doses that have been used in older men in RCTs; the improvements in physical functional measures with replacement doses have been modest.
- Inferences:
  - A higher level of tissue selectivity to improve the benefit : risk ratio.
  - Exercise, cognitive and behavioral may be required to translate muscle mass and strength gains into functional improvements.

Structural Classes of SARMs

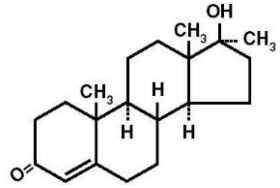
Steroidal SARs Chemotypes

- Removing 19 methyl increases anabolic activity



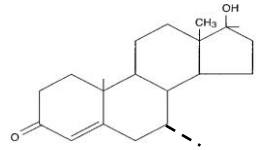
19-nortestosterone

- 17-alpha alkyl substitutions: orally active



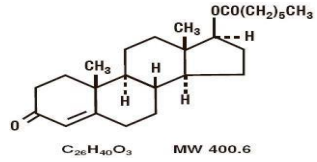
17-alpha methyl T

- 7-alpha alkyl substitutions increase anabolic activity



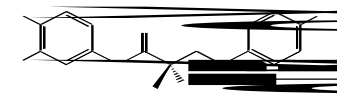
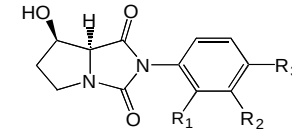
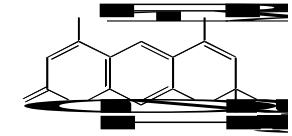
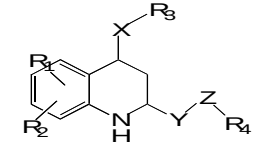
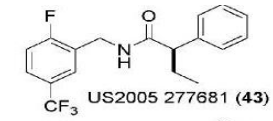
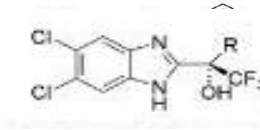
7-alpha alkyl 19-norT

- Esterification of 17-beta hydroxyl group



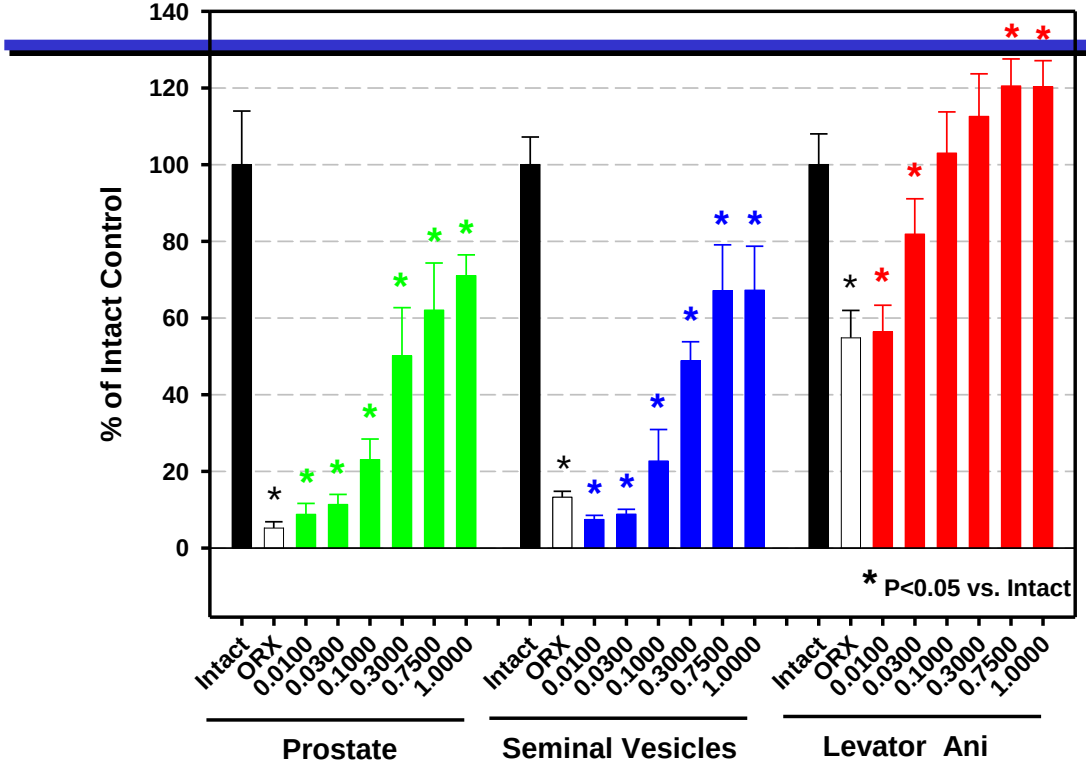
T enanthate

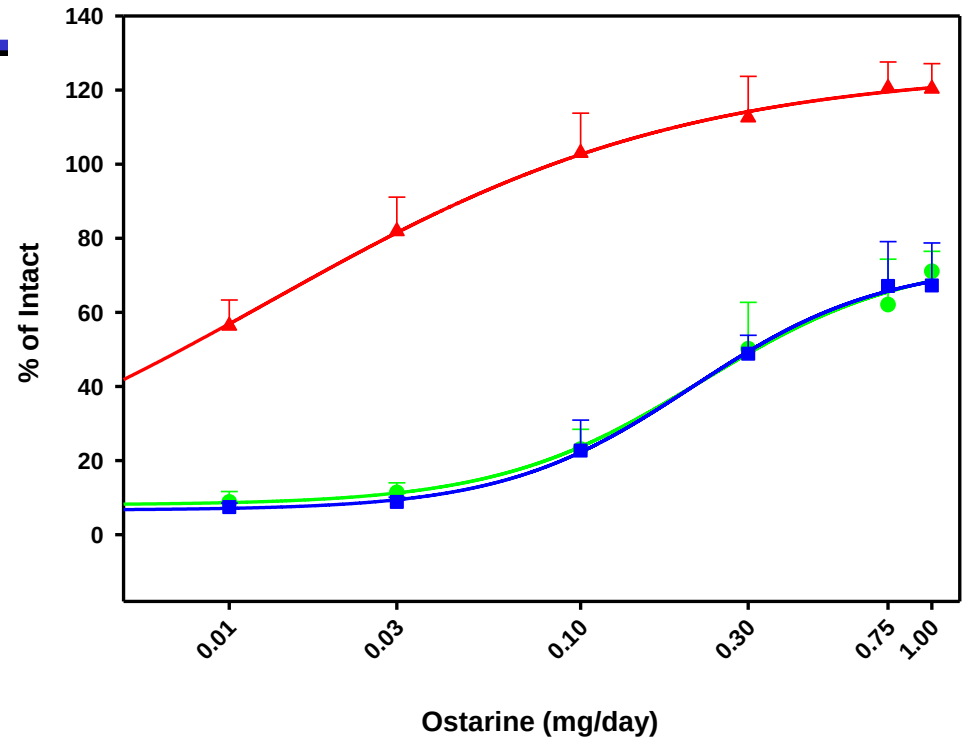
Nonsteroidal SARM Chemotypes

Aryl propionamides		Ostarine, andarine
Bicyclic hydantoins		BMS 564929
Quinolines		Ligand 2226
Tetrahydro-quinolines		S-40503
Benzimidazoles		J & J
Butanamides		Merck

Bhasin S et al. *Nature Endocrinol Metab* 2006;2:146.

Hirshberger Assay: SARMs Selectively Restore *Levator Ani* Mass Relative to Prostate

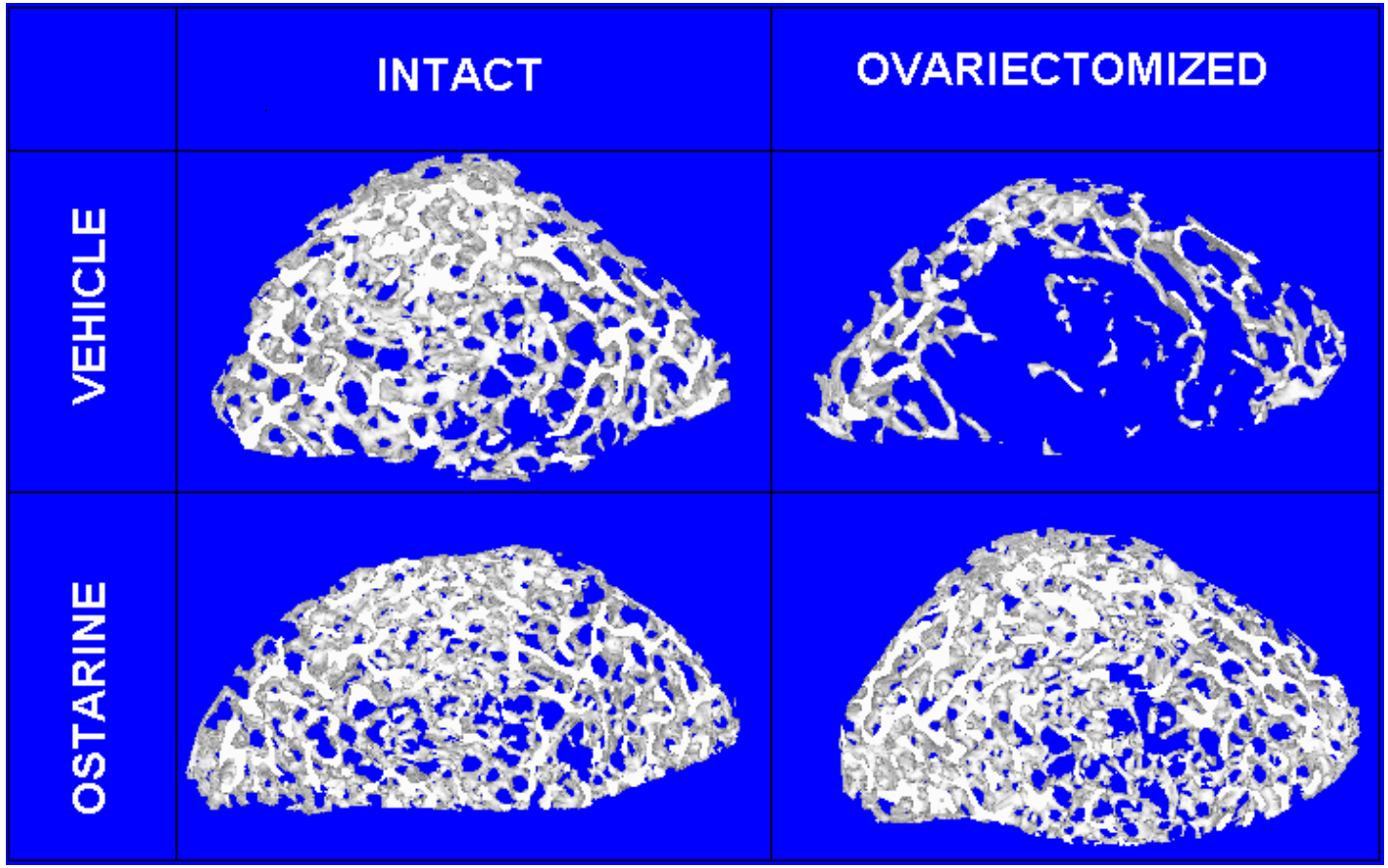




	Prostate	Seminal Vesicles	Levator Ani
E_{max}	75 ± 8	73 ± 3	126 ± 4
ED_{50}	0.22 ± 0.05	0.21 ± 0.02	0.01 ± 0.01

Courtesy: J Dalton.

SARMs Restore Bone Microarchitecture and Bone Strength in Rat Distal Femur

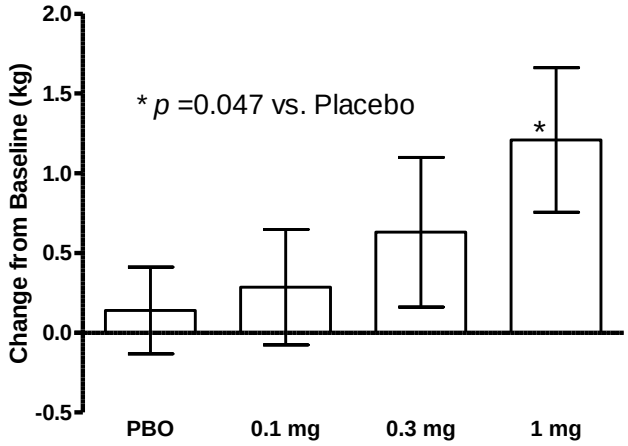


J Dalton. Data presented at 2007 Endo Meeting, Toronto.

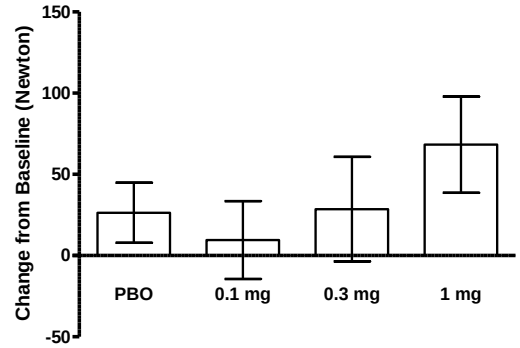
Selective Androgen Receptor Modulators: Effects of LGD-4033 on LBM and Leg Press Strength

28-day Phase 1B Trial

Lean Body Mass

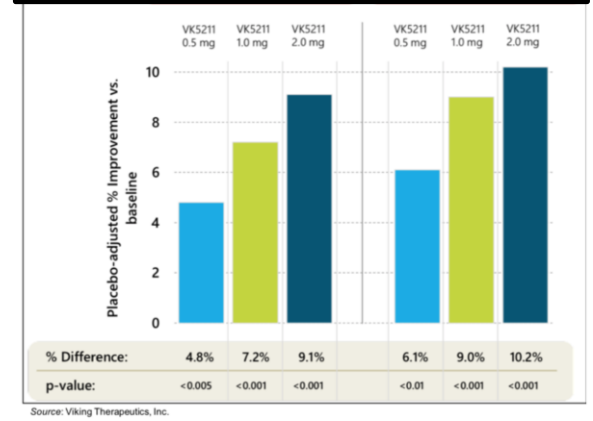


Leg Press Strength



12-Week Phase 2 Trial

Whole Body and Appendicular Lean Mass



Challenge: Designing SARMs that are agonist on the muscle and antagonist on the prostate

Basaria et al, J Gerontol A Biol Sci Med Sci. 2013;68:87-95.

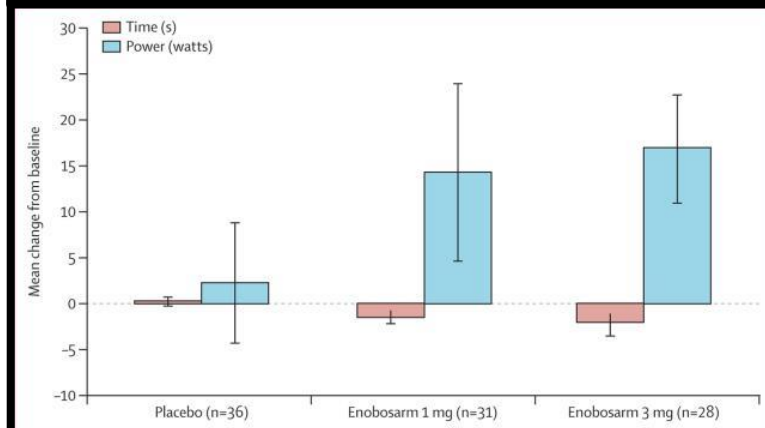
Enobosarm in Cancer Cachexia

Subjects: patients with cancer with > 2% weight loss in 6 months.
Design: placebo, 1 mg, or 3 mg SARM X 113 d
Primary Endpoint: LBM change by DXA

Change in LBM by DXA

	Placebo	1 mg	3 mg
Change in LBM	0.1 (0.7)	1.5 (2.7)	1.1 (1.5)
P	0.44	0.0012	0.046

Change in Stair Climbing Power



Dobs AS, Boccia RV, Croot CC, et al. Lancet Oncol. 2013;14:335-45.

Why Do we not have an Approved SARM on the Market?

In spite of 80 years of empiric human experience from athletes and RCTs, and precedence from approved steroidal SARMs, no nonsteroidal SARM has made it to finish line:

- The non steroidal SARMs have been weak agonists and the doses used in RCTs have been low.
- Trial design issues, relatively small trials, poor execution
- Regulatory issues:
  - Endpoint selection: failure to demonstrate improvements on how the "…*patient lives, feels or functions*"
  - Non-specific off-the-shelf PROs that are not aligned with the condition
  - Poorly crafted "indications"
- Trials have not included an exercise / behavioral intervention

Synthesis and Future Directions

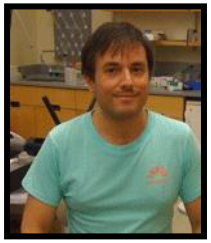
- SARM design: Selective SARMs that are agonist on muscle and antagonist on prostate
- Indications: Consider indications that take advantage of dual anabolic effects and other pleiotropic effects of androgens on mood, wellbeing, amyloid formation, and energy
  - Older adults with UAE and fatigue; or Older adults with MDS
  - Combing with other fall-injury prevention strategies
  - Older adults with Preclinical AD or at high risk of AD
  - Preventing and treating complications of ADT in prostate cancer
- Need **LARGE** trials in functionally-limited older adults
  - Carefully crafted indications
  - Endpoints that accurately measure how a patient "*lives, functions and feels*"
  - Combining performance-based plus self-reported measures of function that are aligned with mechanism of action
  - Combing androgen/ SARM with functional exercise and behavioral intervention
- Additional strategies to achieve tissue-selectivity, increase potency, and improve benefit to risk ratio hold promise

An Investigator's prayer: O Great Spirit! Please, bless my colleagues, who make me look smarter than I am, and soften the hearts of our reviewers.

Clinical Trials
- **Shehzad Basaria**
- Grace Huang
- Anna Ross
- Matt Spitzer
- Rich Eder
- Eric Bachman


Biostatistician
- **Tom Travison**
- **Karol Pencina**


Mechanisms
- **Ravi Jasuja**
- **Wen Guo**
- Carlo Serra
- Rajan Singh


Exercise Physiology
- **Tom Storer**
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- Erin Woodbury
- Jennifer McKinnon

Behavioral Studies
- Peter Gray
- Ray Tricker

Epidemiologic Studies
- Guneet Kaur
- Tom Travison
- Andrea Coviello

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- Liming Peng
- Helene Stroh
- Anqi Zhang

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- Richard Casaburi
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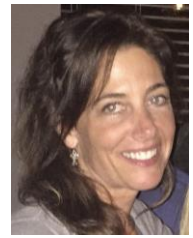
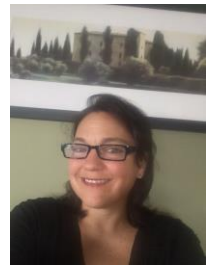
- Kevin Yarasheski
- Fred Sattler
- Stefan Arver
- Fred Wu
- Eric Orwoll



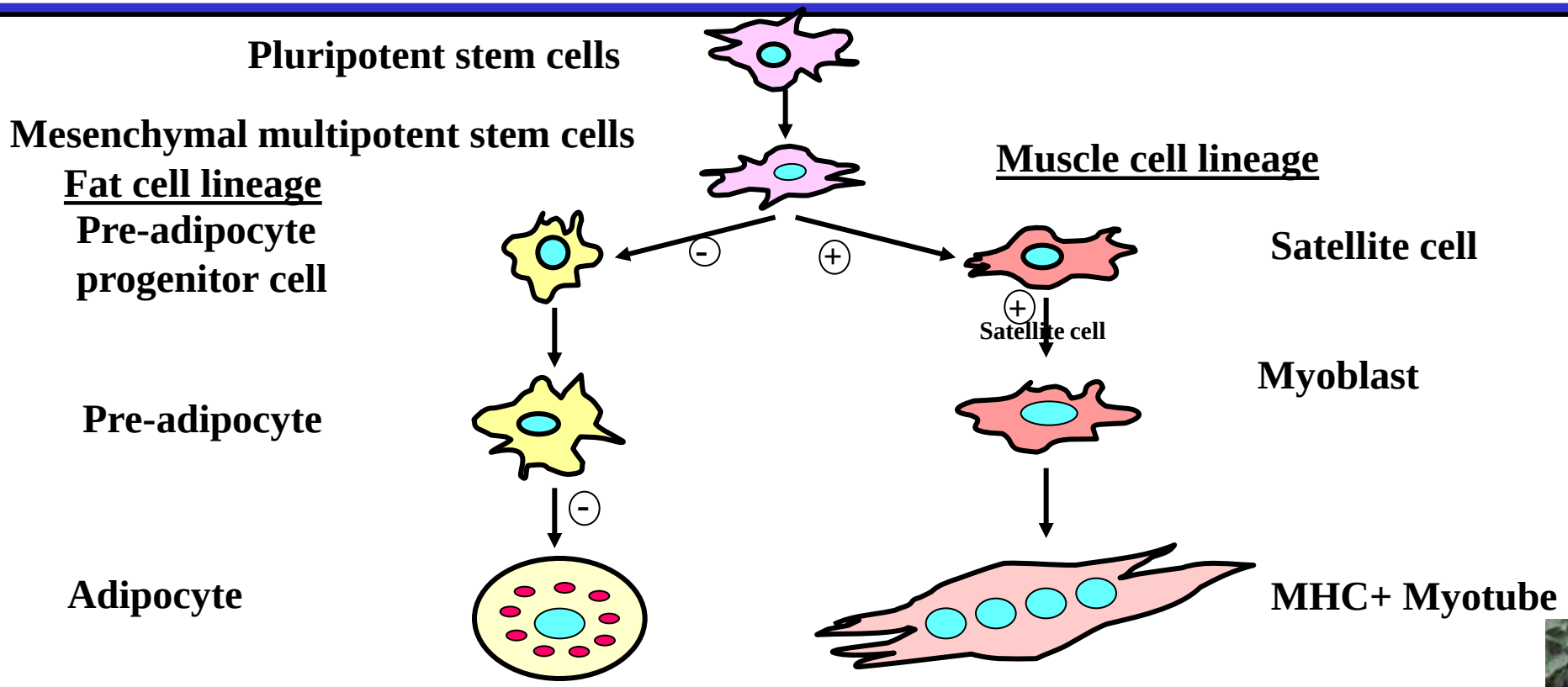



Grant Support: NIA, NINR, NICHD-NCMRR, PCORI, FNIH, Pepper Center P30

Mechanisms of SARM's Tissue Selectivity

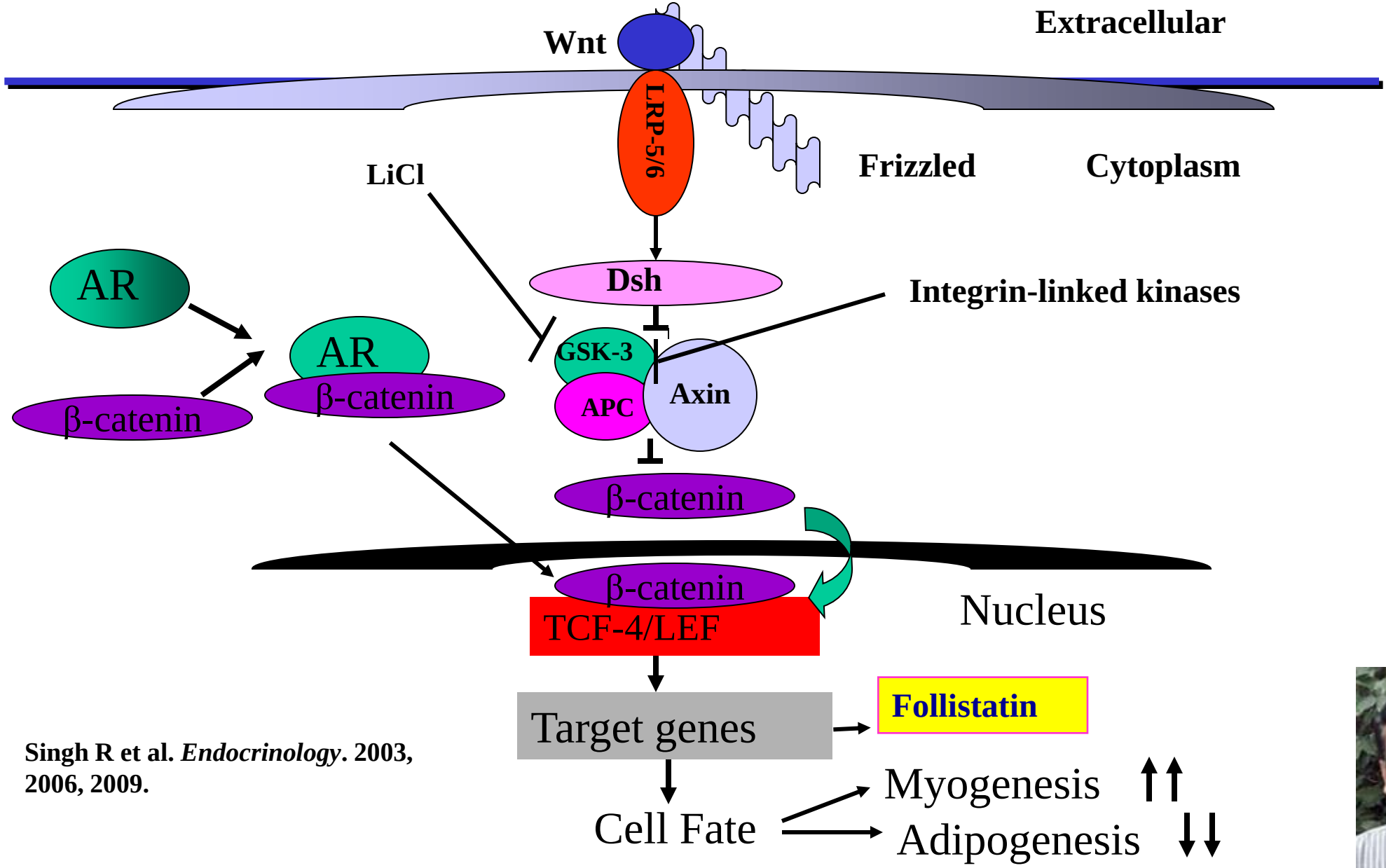
- 5-α reductase hypothesis
- Conformational hypothesis
- Co-activator hypothesis: altered co-activator and N-terminal interaction profile

Mesenchymal Progenitor Cells As Targets of Androgen Action on the Muscle



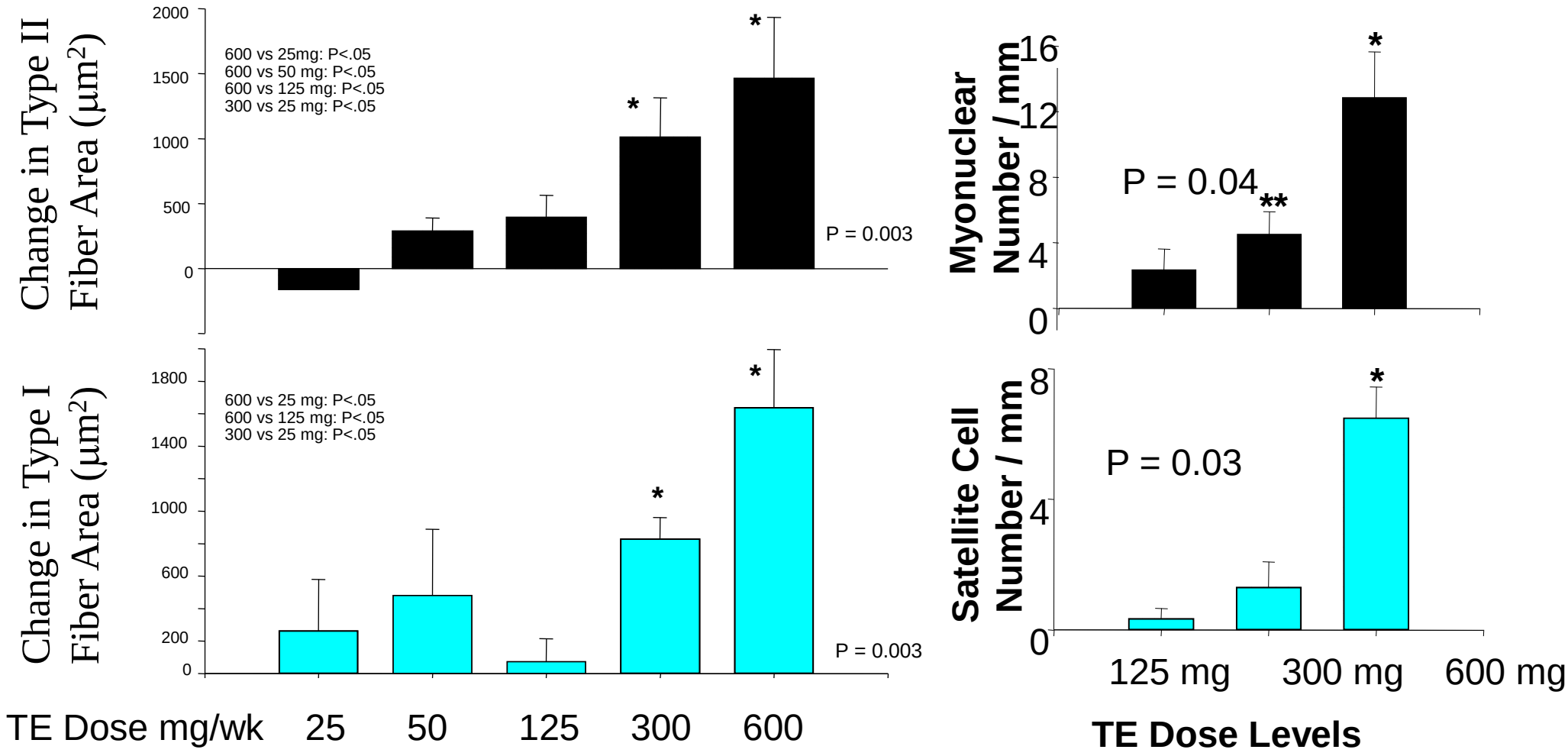
Bhasin S et al. *J Gerontol A Biol Sci Med Sci.* 2003;58:M1103. Singh et al, *Endocrinol* 2003, 2006, 2009

Wnt Signaling Pathway



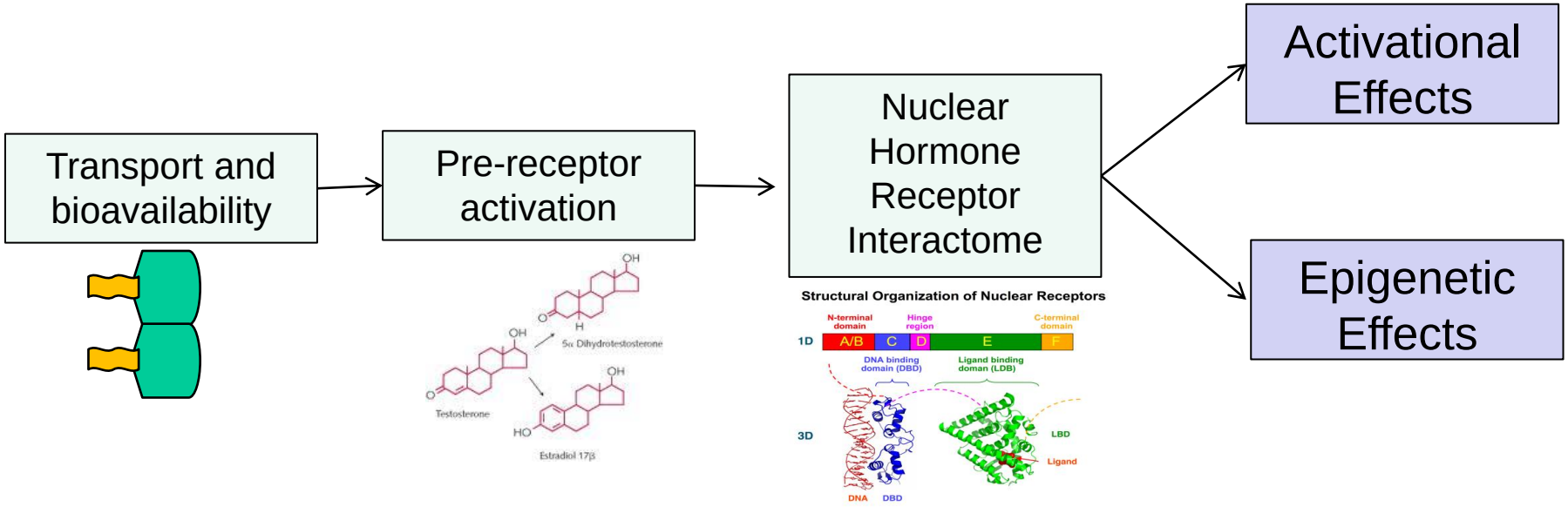
Singh R et al. *Endocrinology*. 2003, 2006, 2009.

Mechanisms of Androgen Action on the Muscle: Testosterone Induces Muscle Fiber Hypertrophy

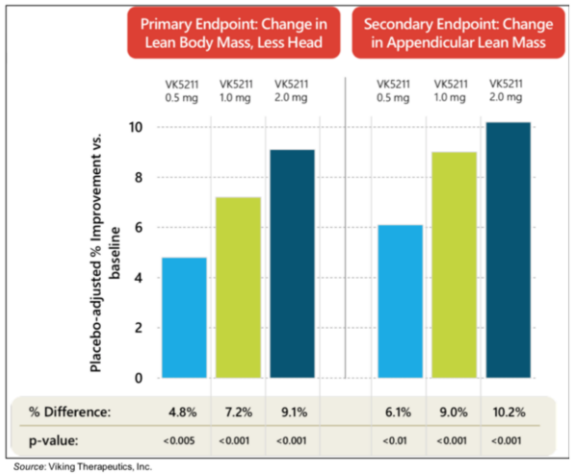


Sinha-Hikim *et al*, Am J Physiol Endocrinol Metab. 2002;283:E154.

Targeting Multiple Levels of AR Interactome to Improve Selectivity and Benefit – Risk Ratio



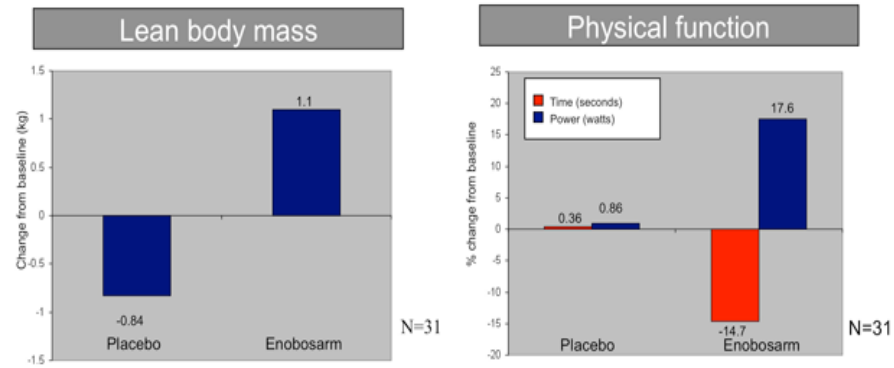
- Pre-receptor level: Testosterone plus 5AR inhibitors
- At the receptor level: tissue selective androgen receptor modulators (SARMs)
- Post receptor level: find signaling molecules, such as follistatin, that are activated by testosterone and promote myogenesis, but are downstream of AR and β-catenin



Source: Viking Therapeutics, Inc.

Phase IIb clinical trial in cancer patients: Enobosarm increased LBM & improved physical function in NSCLC

Subset analysis: 61 NSCLC patients; mean % weight loss at entry was 9.7%



P=0.198

P=0.023; stair climb time
P=0.051; stair climb power

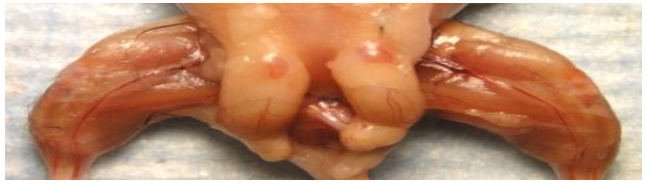
Hypothesis

- Testosterone therapy, when administered in doses that are safe, induces clinically meaningful and patient-important improvements in skeletal muscle mass, muscle performance, physical function and vitality and improves health outcomes.

Spitzer et al, Nature Rev Endocrinol 2013

Recombinant Follistatin Increases Skeletal Muscle Mass, Decreases Whole Body and Visceral Fat, and Spares the Prostate

Lower Extremity Muscles



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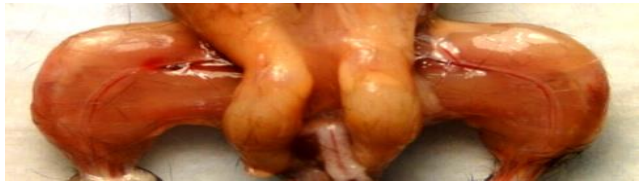

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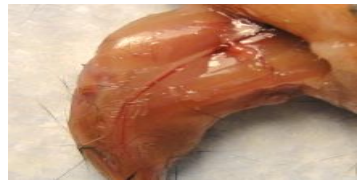

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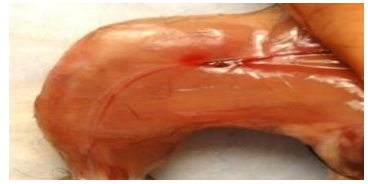
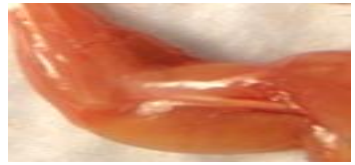


FST 100

Upper Extremity Muscles

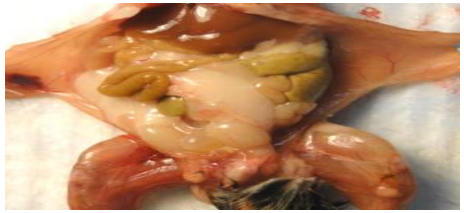
FST 0



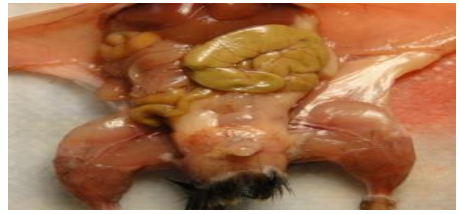
FST 100

Levator ani

Visceral Fat



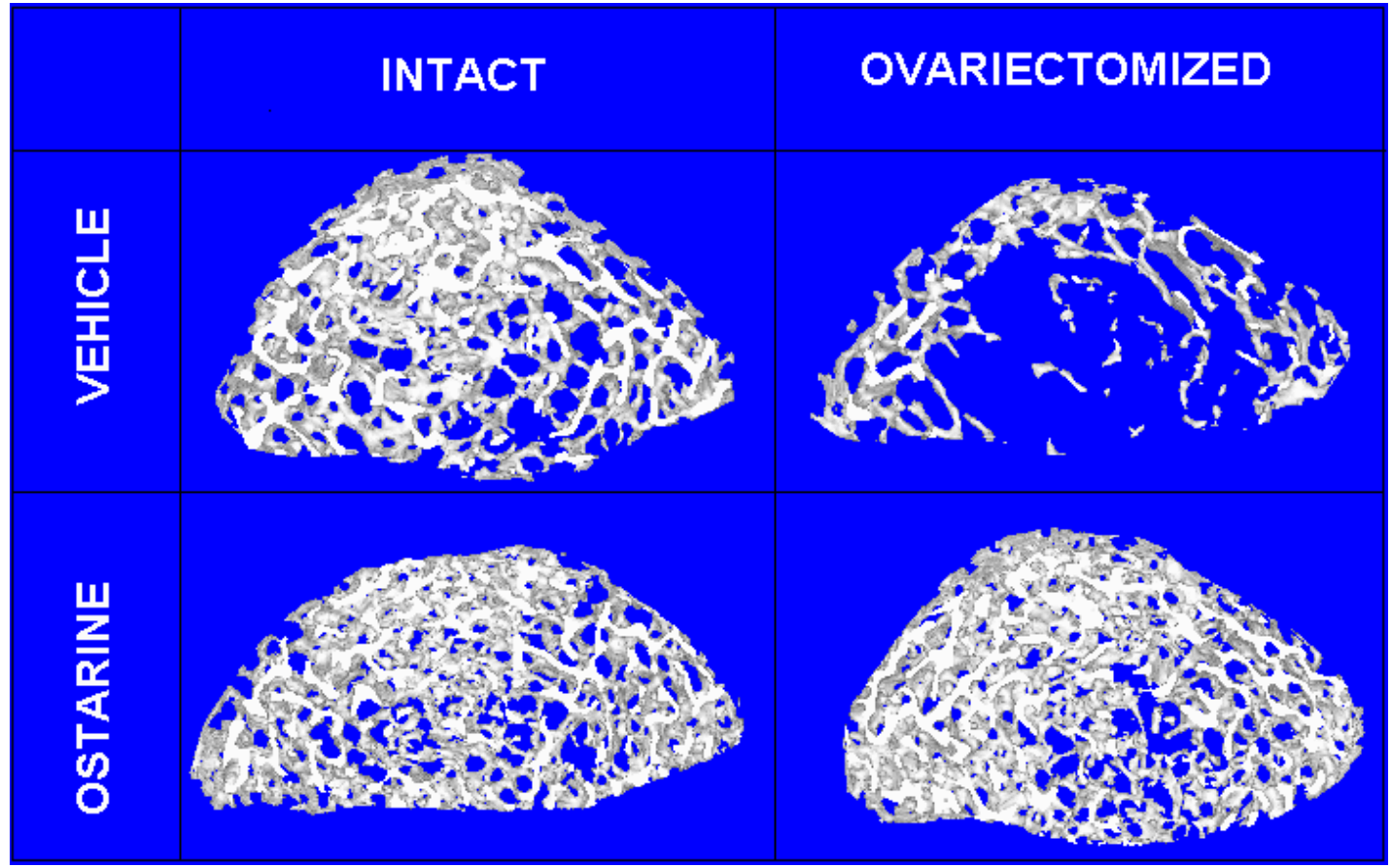
FST 0



FST 100

Rat Distal Femur Reconstructions
(µCT Images From Median Animal in Respective Group)

- Animals were OVX or Sham on Day 0
- Drug administered for 45 days beginning on Day 1
- uCT analysis was performed on a Skyscan 1072 with a nominal resolution of 14 um (~2.5 mm section located
  1.5 mm proximal to the growth plate)



J Dalton. Data presented at 2007 Endo Meeting, Toronto.