

Selective Androgen Receptor Modulators: Current Knowledge and Clinical Applications

Zachary J. Solomon,¹ Jorge Rivera Mirabal, MD,² Daniel J. Mazur, MD,³ Taylor P. Kohn, MD,⁴ Larry I. Lipshultz, MD,^{2,3} and Alexander W. Pastuszak, MD, PhD^{2,5}

ABSTRACT

Introduction: Selective androgen receptor modulators (SARMs) differentially bind to androgen receptors depending on each SARM's chemical structure. As a result, SARMs result in anabolic cellular activity while avoiding many of the side effects of currently available anabolic steroids. SARMs have been studied in the treatment of breast cancer and cachexia and have also been used as performance-enhancing agents. Here, we evaluate and summarize the current literature on SARMs.

Aim: To present the background, mechanisms, current and potential clinical applications, as well as risks and benefits of SARMs.

Methods: A literature review was performed in MEDLINE using the terms selective androgen receptor modulator, hypogonadism, cachexia, breast cancer, benign prostatic hyperplasia, libido, and lean muscle mass. Both basic research and clinical studies were included.

Main Outcome Measure: To complete a review of peer-reviewed literature.

Results: Although there are currently no U.S. Food and Drug Agency-approved indications for SARMs, investigators are exploring the potential uses for these compounds. Basic research has focused on the pharmacokinetics and pharmacodynamics of these agents, demonstrating good availability with a paucity of drug interactions. Early clinical studies have demonstrated potential uses for SARMs in the treatment of cancer-related cachexia, benign prostatic hyperplasia (BPH), hypogonadism, and breast cancer, with positive results.

Conclusion: SARMs have numerous possible clinical applications, with promise for the safe use in the treatment of cachexia, BPH, hypogonadism, breast cancer, and prostate cancer. **Solomon ZJ, Mirabal JR, Mazur DJ, et al. Selective Androgen Receptor Modulators: Current Knowledge and Clinical Applications. Sex Med Rev 2018;XX:XXX–XXX.**

Copyright © 2018, International Society for Sexual Medicine. Published by Elsevier Inc. All rights reserved.

Key Words: Selective Androgen Receptor Modulators; Drug-Related Side Effects and Adverse Reactions; Hypogonadism; Androgens

INTRODUCTION

The androgen receptor (AR) belongs to the superfamily of steroid hormone nuclear receptors, and the binding of its endogenous ligands (ie, testosterone and dihydroxytestosterone

[DHT]) modulates its function as a transcription factor.¹ The effects of the interaction between the AR and androgens are complex and vary depending on sex, age, tissue type, and hormonal status. Although the AR is widely known for its role in male sexual development and maintenance, it also has important effects on bone density, strength, muscle mass, hematopoiesis, coagulation, metabolism, and cognition.^{2,3}

Testosterone and synthetic steroid hormones have found many applications in the clinical setting. One can broadly categorize their effects as anabolic (increased bone density, muscle mass) or androgenic (impaired fertility, virilization, acne). Despite the wide array of medical conditions that potentially could be addressed with the supplementation of steroid hormones, their therapeutic use is often curtailed owing to potential side effects, including erythrocytosis, prostate hypertrophy, hepatotoxicity, aromatization to estrogen, and testicular

Received May 3, 2018. Accepted September 21, 2018.

¹Baylor College of Medicine, Houston, TX, USA;

²Scott Department of Urology, Baylor College of Medicine, Houston, TX, USA;

³Urology Associates, Denver, CO, USA;

⁴Brady Urological Institute, Johns Hopkins School of Medicine, Baltimore, MD, USA;

⁵Center for Reproductive Medicine, Baylor College of Medicine, Houston, TX, USA

Copyright © 2018, International Society for Sexual Medicine. Published by Elsevier Inc. All rights reserved.

<https://doi.org/10.1016/j.sxmr.2018.09.006>

atrophy.⁴ The use of testosterone therapy in prostate cancer (PCa) is a topic of controversy and was debated in an article by Jannini et al.⁵ The authors conclude that PCa is indeed testosterone dependent. However, AR saturation in the prostate is thought to occur at subphysiologic serum testosterone levels (60–120 ng/dL). As such, increases in serum testosterone levels above this concentration are not expected to result in further AR activation and activity.⁶ There is no conclusive evidence demonstrating an increased risk of PCa in the setting of testosterone therapy. Of interest, Gravina et al⁷ demonstrated a significant reduction in the tumor growth of PCa cells in the setting of supraphysiologic intraprostatic testosterone concentrations.

Selective androgen receptor modulators (SARMs) are small-molecule drugs that can exert varying degrees of both agonist and antagonist effects on ARs in different tissues. Their actions can be understood by considering the selective estrogen receptor modulators (SERMs) that preceded them. One SERM widely used to treat breast cancer, tamoxifen, acts as an antagonist in the breast, an agonist in the bone, and a partial agonist in the uterus. The tissue-specific effects of these agents are precisely what makes them attractive, because they can be tailored to address specific medical conditions while minimizing off-target effects.

Basic laboratory experiments have sought to investigate and optimize the pharmacodynamic and pharmacokinetic properties of SARMs according to their desired site of action. SARMs have been chemically engineered to more specifically target AR function in certain tissues while minimizing off-target effects.⁸ There is minimal variation between AR structure, but the regulatory milieu of each tissue allows SARMs to possess relative tissue specificity. Animal models have been used to investigate the effect of SARMs on skeletal muscle in both eugonadal and hypogonadal rats.⁹ Animal models of muscular dystrophy have been used to investigate the use of SARMs in muscle pathology, demonstrating encouraging results.^{9,10} SARMs have also been trialed as reversible hormonal contraceptives in rats.¹¹ Although still preliminary studies, researchers have investigated the possible use of SARMs in Alzheimer's disease, PCa, benign prostatic hyperplasia (BPH), and osteoporosis.^{12–14} SARMs have begun to be studied in the preclinical and clinical phases as treatment options for cancer-related cachexia, breast cancer, BPH, and hypogonadism.^{2,15,16} There are several ongoing Phase 1 and Phase 2 clinical trials investigating the use of SARMs.

In this review, we present the background, mechanisms, and current and future clinical applications of SARMs. We also consider the risks and benefits of SARMs and discuss their potential for misuse.

METHODS

A literature review was performed in the PubMed/Medline database using the terms selective androgen receptor modulator, hypogonadism, cachexia, breast cancer, benign prostatic hyperplasia, and lean muscle mass. Both basic and clinical studies were included.

Currently ongoing clinical trials listed on <http://www.clinicaltrials.gov> that are investigating SARMs were reviewed as well.

HISTORY OF SARMs

An improved understanding of SERMs and their mechanisms of action in the 1990s, as well as the growing use of tamoxifen in the treatment of breast cancer, stimulated interest in analogous drugs to modulate the AR.^{17,18} Several laboratories began working on identifying lead candidates and specific pharmacophores, with early work centered around a class of aryl-propionamides identified from hydroxyflutamide analogs in 1998.¹⁵ Over the past 20 years, the number of bioactive SARMs under investigation has continued to grow, as has our knowledge of their mechanisms of action.

BIOCHEMICAL AND BASIC SCIENCE BACKGROUND

As demonstrated by the development and clinical use of SERMs such as tamoxifen, the key characteristic underlying the therapeutic potential of SARMs is their tissue specificity. While steroid hormone replacement therapy offers many benefits, it can be associated with a high rate of adverse effects (AEs), partly owing to widespread and non-specific activation of the AR in many different tissues. The most basic distinction in tissue selectivity lies between anabolic and androgenic effects of steroids and their analogs, with the former being responsible for trophic effects on bone and muscle and the latter having effects on the development and physiology of the genitourinary system.⁴

The AR functions as a nuclear steroid hormone receptor. Its ligand enters the cell, typically by diffusion, and encounters the unoccupied AR in the cytoplasm.¹ Upon binding, the AR dissociates from cytosolic heat shock proteins and migrates to the nucleus where it associates with various coregulatory proteins.¹ The complex then interacts with specific DNA sequences and acts as a transcriptional regulator of androgen-responsive genes.^{1,19} The intricate and tissue-specific process dictates the transcriptional and thus the cellular response.^{19,20} Much work has been focused on determining how different SARMs achieve tissue specificity and partial agonism, though the exact mechanisms remain unclear.²⁰

Hikichi et al²⁰ helped elucidate the mechanisms of tissue specificity in 2015 by investigating an experimental SARM, TSAA-291. Using reporter assays, a method to assess the degree to which a transcription factor activates target genes, the investigators compared DHT and TSAA-291.²⁰ While nearly identical gene responses were observed using reporter assays for skeletal muscle cells, TSAA-19 agonist activity in prostate cells was approximately half that of DHT.²⁰ Thus, despite binding to ARs in the same tissues, TSAA-291 displayed a different cellular response than DHT in the prostate. This phenomenon was partly explained by the demonstration that TSAA-291 led to a different cofactor recruitment in the prostate and thus different

downstream effects.²⁰ This observation suggests that conformational variations in ligand–AR complexes are at least partially responsible for the unique cellular responses.^{1,20} This is further supported by the findings of Unwalla et al,⁴ who demonstrated that small variations in SARM conformation can result in substantial effects on activity.

Indeed, the AR is a modular protein with discrete domains responsible for different functions.²¹ The AR is maximally active across different tissues when a ligand promotes interactions between the N- and C-terminal AR domains.²¹ This is supported by observations that mutations in the AR that disrupt this interaction lead to incomplete virilization in patients.²¹ Schmidt et al²¹ showed that the ability to reduce N/C interactions is the hallmark of SARMs that display antagonism in androgenic tissues.

Thus, it seems that the ability of SARMs to signal via the AR depends on how their unique conformations interact with the functional domains of the AR, and in turn how those domains interact with the cellular regulatory milieu to target DNA expression. Given that each SARM–AR complex has a different conformation and that tissues have unique patterns of AR expression, coregulatory proteins levels, and transcriptional regulation, one can imagine the immense diversity and potential for tissue- and action-specific SARMs.¹ Figure 1 shows a simplified SARM-induced signaling pathway.

Given the complex biologic actions of steroid hormones and SARMs depending on binding affinity and degree of agonism

and antagonism at the AR in different tissue types, high throughput screening methods are being used to discover SARMs with favorable biologic and pharmacokinetic profiles.⁸ For example, Unwalla et al⁴ recently published a new SARM compound based on a novel cyanopyrrole structure that selectively promotes muscle growth while having limited androgenic effects in an orchidectomized rat model. Miller et al¹ reported on RAD-140, a potent anabolic SARM with antagonistic effects on the prostate and seminal vesicles, qualities that would make it well suited to treat conditions such as BPH while targeting muscle and bone growth. As will be discussed, the optimization of tissue specificity and downstream signaling continues to broaden the potential application of SARMs for contraception, osteoporosis, cachexia, muscular dystrophies, PCa, and Alzheimer's disease.

THERAPEUTIC PROMISE OF SARMs

Male Contraception

SARMs show promise for use as a method of male contraception in animals. Exogenous testosterone interferes with spermatogenesis via negative feedback on the hypothalamic–pituitary–gonadal (HPG) axis.^{11,22} Chen et al¹¹ demonstrated that administration of a SARM, C-6, markedly suppressed spermatogenesis and reduced peripheral testosterone levels while decreasing testicular and epididymal size. Similar experiments by Jones et al²³ using a SARM, S-23, combined with estradiol

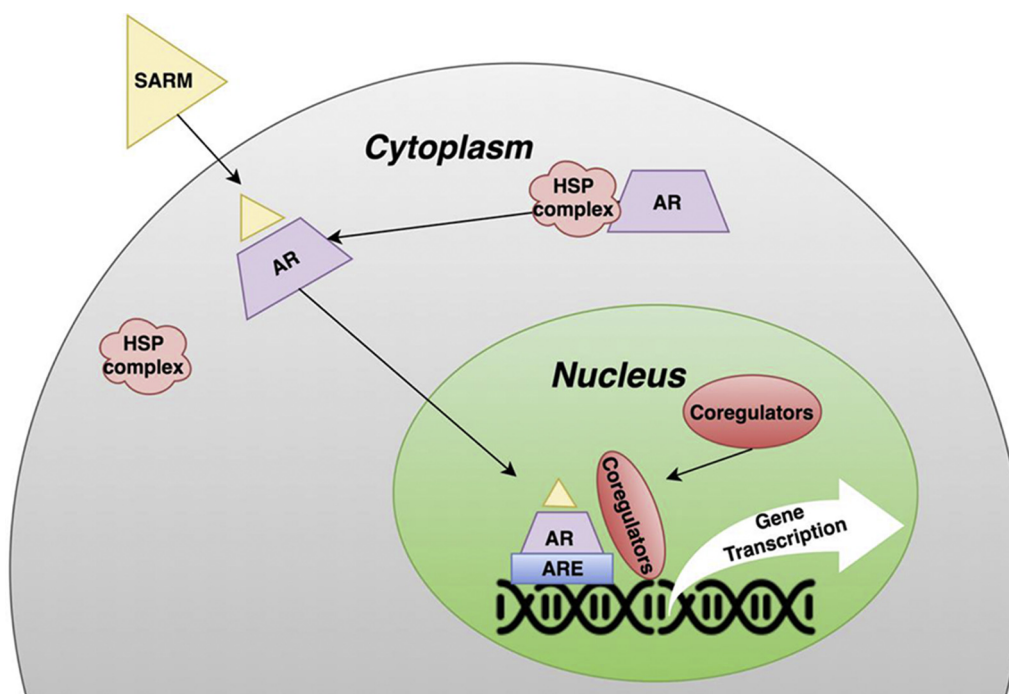


Figure 1. Mechanism of selective androgen receptor modulator (SARM) signaling. Like androgens, SARMs enter the cytoplasm, where they displace the androgen receptor from heat shock proteins. Once bound, they translocate to the nucleus and act as transcription factors by binding androgen response elements (AREs). Depending on the tissue type and regulatory environment of the cell, different coregulatory proteins help determine and modulate the transcriptional response. AR = androgen receptor; ARE = androgen response element. HSP = heat shock protein.

benzoate, demonstrated a completely reversible effect on the suppression of spermatogenesis and serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels. During the experiment, 4 of 6 rats demonstrated a complete absence of testicular sperm with no pregnancies observed in mating trials. Once treatment was stopped, mice regained fertility with 100% subsequent pregnancies (6/6) within 100 days after treatment cessation.²³ Notably, S-23 also increased lean muscle mass, bone mineral density, and decreased fat mass in mouse models.²³

Osteoporosis

Many SARMs have trophic effects on bone.¹² Watanabe et al¹² investigated a novel SARM, BA321, which displays binding to both AR and estrogen receptors (ER) without androgenic effects, and can completely restore bone loss in orchidectomized mice. This raises the possibility that a host of different SARMs could prove to be especially effective as adjuncts in treating osteoporosis or other conditions that lead to suboptimal bone density and mineralization.

Prostate Cancer

PCa may also be addressed by SARMs. Pekka et al²⁴ recently published mouse data showing that a new SARM, FL442, reached high tissue concentrations in the prostate and acted as an AR antagonist in PCa cell models with efficacy comparable to that of enzalutamide, an antiandrogen used in the treatment of castration-resistant PCa. Notably, FL442 maintained the ability to prevent cell proliferation even in cell lines with AR mutations that conferred resistance to enzalutamide.²⁴ Likewise, work by Schmidt et al²⁵ focused on MK-4541, which induces caspase-3 activity and apoptosis in androgen-independent, AR-positive PCa cell lines while sparing AR- and AR+ non-PCa cells. Chisamore et al¹³ also demonstrated that administration of MK-4541 resulted in a decrease in plasma testosterone levels, likely through AR-mediated negative feedback signaling through the HPG axis. These results support the promise of SARMs in treating hormone ablation-resistant disease through the activation of AR-induced expression profiles that are toxic to cancer cells while avoiding the negative effects of traditional antiandrogen therapies.

Another possible application for SARMs in PCa management is tissue-targeted imaging.²⁶ Given that the AR is expressed in all stages of PCa evolution, radioactive iodine-labeled SARMs that achieve high intraprostatic concentrations could be used for radiologic diagnosis, especially for metastatic disease.²¹

Sexual Medicine

Androgens have important effects on sexual functions in both men and women, a fact consistent with the expression of the AR in the genitourinary systems of both sexes.^{27–29} Although today the treatment of postmenopausal genitourinary symptoms (PGS) in women is typically centered on estrogen-based therapies,

historically both androgens and estrogens were used.²⁸ Indeed, recent double-blind placebo-controlled clinical trials have shown that local vaginal application of dehydroepiandrosterone improves postmenopausal symptoms, including moderate to severe dyspareunia.^{28,30} Several studies have evaluated the effects of local vaginal testosterone application, with effects ranging from lower vaginal pH, increased lactobacilli, and improved vaginal maturation index.²⁸ Several clinical trials using transdermal testosterone for female sexual dysfunction in women with low serum testosterone showed improvements in sexual desire, pleasure, and orgasms.³¹ For example, treatment with testosterone patches in women with hypoactive sexual desire disorder after bilateral salpingo-oophorectomy increased episodes of satisfying sexual encounters and increased sexual desire.³²

Given the evidence surrounding the utility of androgens in treating PGS and hypoactive sexual desire in women, SARMs represent a potentially attractive future therapy. Indeed, studies in ovariectomized rats showed that treatment with several halogenated candidate SARMs (S-23, S-24, S-27) led to significant increases in sexual motivation, and the use of other SARMs led to an increase in myometrial thickness to greater than control.³¹ This evidence suggests that SARMs could be designed for specific effects on either female libido or reproductive organs.

In men, there is little controversy surrounding the critical role of testosterone in male libido and sexual function. Many trials and studies have established the sexual benefits of exogenous testosterone use for men. For example, in a cohort of hypogonadal men treated chronically with testosterone gel, scores quantifying sexual desire, enjoyment, erection quality, and sexual activity were all markedly and sustainably improved from baseline.³³ Similar to the preclinical data discussed previously in regard to SARMs and female sexual function, treatment of male rats with SARMs led to increased sexual behavior.³⁴ Male rats treated with LGD226, a synthetic SARM, displayed an increased number of mounts, intromissions, and ejaculations compared with a control group. These results were not significantly different from a group treated with fluoxymesterone, a synthetic androgen. These results suggest that SARMs could be as effective as treatment with testosterone and its derivatives in promoting male libido. More research is needed to investigate the effect of SARMs on sexual desire and function in humans of both sexes.

Benign Prostatic Hyperplasia

Modulation of the AR using SARMs could also have a role in treating benign prostatic hyperplasia (BPH), primarily via immunomodulatory mechanisms.³⁵ Vignozzi et al³⁶ demonstrated that activation of the AR by DHT leads to a reduced inflammatory response in cultured human prostatic stromal cells. Another article from the same institution evaluated the role of testosterone on prostate inflammation induced by a high-fat diet in a rabbit model.³⁶ The authors found that testosterone supplementation normalized inflammatory changes in the prostate by inhibiting fibrosis and myofibroblast differentiation. SARMs

may be attractive in BPH treatment as they modulate the AR. Nejjishima et al¹⁶ compared the use of flutamide with S-40542, a novel SARM, in a rat model of BPH. Both agents similarly decreased prostate weight in a dose-dependent manner, but S-40542 had a weaker effect on the levator ani muscle than flutamide.¹⁶ Additionally, S-40542 showed no effect on testosterone or LH levels, both of which were increased by flutamide.¹⁶ A different study by Gao et al³⁷ compared S-1 and S-4, both SARMs, with finasteride and hydroxyflutamide for the treatment of BPH in a rat model. Both finasteride and S-1 selectively decreased prostate weight to a similar extent without changes to the levator ani muscle or to plasma testosterone, FSH, or LH levels, all of which were altered by treatment with hydroxyflutamide.³⁷ S-1 and S-4 decreased 5- α -reductase levels weakly, suggesting that they reduced prostate size via a different mechanism than finasteride.³⁷ These results raise the possibility of future SARMs as adjuncts to or monotherapy for BPH, with minimal side effects.

Alzheimer's Disease

Hypogonadal men demonstrate a decrease in various cognitive processes, including episodic memory, working memory, processing speed, visual spatial processing, and executive function.^{38,39} These functions are partially regulated by regions of the brain that are modulated by the AR.⁴⁰ Moffat et al⁴¹ performed a subanalysis of the Baltimore Longitudinal Study of Aging that included 407 men without dementia who were followed for a mean of 9.7 years. Study subjects underwent medical, physiological, and neuropsychological evaluations as well as laboratory testing for total testosterone and steroid hormone binding globulin. Free testosterone index was calculated based on total testosterone and steroid hormone binding globulin levels. Results showed that higher free testosterone index was associated with better scores on visual and verbal memory, visuospatial functioning, visual-motor scanning, and a reduced rate of longitudinal decline in visual memory.

As we continue to elucidate the effects of testosterone on cognition, we can appreciate that SARMs may one day play a role in the treatment of cognitive disorders such as Alzheimer's disease. Androgen depletion is considered a significant risk factor for Alzheimer's disease, and circulating testosterone levels are inversely correlated with levels of amyloid β ($A\beta$) in the brains of elderly men.¹⁴ Androgens suppress the accumulation of $A\beta$ by upregulating expression of neprilysin, which degrades amyloid.¹⁴ Akita et al¹⁴ recently demonstrated that a novel SARM, NEP28, increases the activity of neprilysin in addition to having systemic anabolic effects with reduced androgenic effects.

Muscular Dystrophy

Another group of diseases that may benefit from interventions with SARMs is the muscular dystrophies. Pilot studies using oxandrolone in boys with Duchenne muscular dystrophy (DMD) demonstrated gains in muscle mass and protein

synthesis, but hepatotoxicity and off-target effects on genitalia were major treatment-limiting side effects.⁹ Cozzoli et al¹⁰ demonstrated the efficacy of GLPG0492, a novel SARM, in a mouse model of DMD. Groups of mice were treated with GLPG0492, methylprednisone, or nandrolone. Mice treated with GLPG0492 showed preserved running performance, increases in maximum isometric diaphragm contractile force, and decreased muscle fibrosis.¹⁰ SARMs administered to patients with DMD would theoretically increase muscle mass and protein synthesis levels comparable to that observed with oxandrolone, without the off-target side effects.

Cachexia

One of the most promising potential applications of SARMs include conditions in which cachexia is a consequence of the disease state or its therapy, including human immunodeficiency virus, cancer, immobilization, and chronic glucocorticoid use.⁴² In healthy individuals, muscle exists in a state of equilibrium between breakdown and synthesis, and any alteration to the rate of degradation or protein synthesis can favor atrophy or hypertrophy. Efforts attempting to elucidate the cellular mechanisms by which SARMs promote tissue anabolism are ongoing. Shankaran et al⁴³ used a proteome-wide muscle protein fractional synthesis analysis to demonstrate that SARM treatment in an ovariectomized rat model resulted in an increase in synthesis of contractile proteins such as myosin and actin, and also a small but significant increase in muscle mitochondria biogenesis. Research on GTx-024 (Enobosarm) by Dubois et al⁴⁴ in AR knockout satellite cell lines suggests that SARMs also mediate muscle hypertrophy via AR action on vimentin-positive resident muscle fibroblasts, likely through upregulation of paracrine growth factor signaling. Jones et al⁴² demonstrated that in a rat model of dexamethasone and castration-induced muscle atrophy, both testosterone and S-23, a SARM, reduced muscle atrophy. Rats were divided into 4 groups and given either vehicle, dexamethasone alone (Dex) to induce muscle atrophy, or dexamethasone plus either testosterone or S-23.⁴² Activity of intracellular growth pathways was then analyzed.⁴² Both testosterone and S-23 treatment in the Dex model blocked dephosphorylation and thus inactivation of proteins in the PI3/Akt kinase cascade.⁴² These signaling pathways are involved in cellular growth and protein synthesis and upregulate the production of downstream targets including mTOR and glycogen synthase kinase.⁴¹ Testosterone and S-23-based treatment of the Dex-model mice also blocked the upregulation and activation of ubiquitin ligases and other proteins that increase cell catabolism, including MAFbx, MuRF1, and FoxO.⁴² The overall effect of S-23 and testosterone treatment was to attenuate the catabolic effects of dexamethasone administration.⁴² Finally, a similar experiment was performed in castrated mice to evaluate if S-23 could rescue the mice from castration-induced muscle atrophy.⁴² Treatment of the castrated mice led to hypertrophy of the levator ani muscle compared with eugonadal controls, with attenuation of castration-induced reductions in IGF-1 concentrations.⁴²

Similar results were observed in a mouse model of hind limb immobilization.⁴⁵ Taken together, these results support the conclusion that SARMs may reverse and prevent iatrogenic and disease-induced catabolism while having minimal effect, or a beneficially antagonistic effect, on androgenic tissues.

Breast Cancer

SARMs may be useful in the treatment of breast cancers that express AR.⁴⁶ Up to 85% of estrogen receptor (ER)-positive breast cancers and 95% of ER-negative breast cancers express AR.⁴⁷ AR-positive tumors are associated with improved overall survival and disease-free survival when compared with AR-negative tumors.⁴⁶ ARs in breast cancer likely confer survival advantage by modulating ER signaling, which may reduce the risk of metastasis and aggressive disease.⁴⁷ There is currently a clinical trial in the recruitment phase seeking to evaluate pembrolizumab and enobosarm cotherapy for the treatment of AR-positive metastatic triple negative breast cancer.⁴⁸

Field Leader? Enobosarm Trials

Several clinical trials are assessing the application of SARMs as novel treatment agents for cancer-related cachexia, breast cancer, stress urinary incontinence, and PCa.^{15,16} A summary of current clinical trials listed on <http://www.clinicaltrials.gov> using SARMS can be found in Table 1. As discussed, unique SARMs are being designed to have maximum action at the desired tissue with minimal or antagonistic effects on other tissues, widening the spectrum of potential therapeutic viability in a variety of clinical conditions. Although there are no U.S. Food and Drug Agency (FDA)-approved SARMs available for clinical use, enobosarm has played a central role in several clinical trials.⁴⁹

120 healthy elderly men and postmenopausal women participated in a 12-week double-blind, placebo-controlled Phase 2 clinical trial involving enobosarm with 5 dosing groups: placebo, 0.1 mg, 0.3 mg, 1 mg, and 3 mg of enobosarm.³ The primary end point was total lean body mass (LBM), and secondary end points included physical function, insulin resistance, body weight, and drug safety.³ At the highest dosing group (3 mg), subjects taking enobosarm saw an average increase in LBM of 1.3 kg, with a 0.6 kg decrease in fat mass.³ Subjects on enobosarm also had dose-dependent improvements in physical function as measured by stair-climbing time, significant reductions in blood glucose, and a trend toward lower blood insulin levels.³ Although serum triglycerides trended downward in subjects taking enobosarm, there were dose-dependent reductions in high-density lipoproteins (HDL) of up to 27% in the 3 mg enobosarm group.³ Men were also found to have significant but expected decreases in sex hormone binding globulin (SHGB), but no changes in free testosterone, DHT, estradiol, FSH, or LH levels.³ Women had similar decreases in SHGB, but with significant reductions in LH and FSH.³ No changes were observed in total bilirubin, gamma-glutamyl transferase, or alkaline phosphatase for any dose of enobosarm, but small increases in hemoglobin

and transient increases in alanine aminotransferase (ALT) were seen in 8 subjects, 7 of which resolved by the end of the 12 weeks.³

A second randomized, double-blind, placebo-controlled Phase 2 trial evaluated the use of enobosarm in 159 patients with cancer-related cachexia.⁵⁰ Men and postmenopausal women with cancer and over 2% weight loss over 6 months were randomized to take placebo, 1 mg, or 3 mg of enobosarm for 113 days.⁵⁰ Both the 1-mg and 3-mg groups saw increases in LBM, with decreased stair-climbing times.⁵⁰

Given these results, the Prevention and Treatment of Muscle Wasting in Cancer Patients (POWER) trials, 2 identical randomized double-blind, placebo-controlled Phase 3 trials were designed to assess the ability of enobosarm to prevent and treat cachexia in patients with stage 3 and 4 non-small-cell lung cancer.² However, both trials failed to meet the primary end points of improvements in LBM and assessments of physical function after showing mixed results.^{47,51} Currently enobosarm is being assessed in a different Phase 2 trial to examine its effect on stress urinary incontinence in postmenopausal women (Table 1).

Safer Than Testosterone?

Testosterone therapy (TTh) is currently the mainstay treatment for hypogonadism and is an option for treating cancer-related cachexia.^{15,52} Although TTh is effective in treating hypogonadal symptoms, it possesses potential side effects that require careful monitoring.⁵² TTh can lead to gynecomastia owing to estrogen aromatization, erythrocytosis, reduced spermatogenesis, acne, male pattern baldness, and undesirable alterations in serum lipids, among other effects.⁵²

Compared with steroidal androgens, SARMs appear to be much better tolerated with few incidences of severe AEs. In addition, many of these preclinical agents can be administered as oral therapies. This helps to reduce the risk of accidental exposure, as can be seen with topical testosterone, and can significantly improve ease of administration compared with currently available forms of TTh.^{2,3,15,44} As described above, enobosarm treatment led to small increases in hemoglobin in certain subjects, increases in ALT, and decreased serum HDL levels. Other early clinical studies have investigated the safety profiles and pharmacodynamics and kinetics of several candidate SARMs.

GSK2881078, a SARM being investigated by GlaxoSmithKline for muscle growth and strength in subjects with muscle wasting, was tested in a 2-part, randomized, double-blind, placebo-controlled dose-escalation Phase 1 study to assess safety, pharmacokinetics, and pharmacologic effects in a small cohort of young men and postmenopausal women.⁵³ Overall the treatment was well tolerated, with the most common adverse events being constipation, dyspepsia, and nausea (3 of 89).⁵³ 1 female subject developed a maculopapular rash with biopsy consistent with a

Table 1. SARM Review Tables

Study Title	ClinicalTrials.gov Identifier	Phase	Design	Intervention	Patient Population	Primary Outcome	Status
Pembrolizumab and Enobosarm in Treating Patients with Androgen Receptor Positive Metastatic Triple Negative Breast Cancer	NCT02971761	Phase 2	Intervention model: single group assignment	Enobosarm + Pembrolizumab	Patients with metastatic triple negative breast cancer	Safety and tolerability of treatment, response rate	Recruiting; estimated primary completion June 2018
Study to Assess Enobosarm (GTx-024) in Postmenopausal Women with Stress Urinary Incontinence (ASTRID)	NCT03241342	Phase 2	Randomized placebo controlled	Enobosarm vs placebo	Post-menopausal women aged 18–80 with stress urinary incontinence	Change in number of stress urinary incontinence episodes	Not yet recruiting
A Selective Androgen Receptor Modulator For Symptom Management in Prostate Cancer	NCT02499497	Phase 2	Randomized placebo controlled trial	LY2452473 vs placebo	Men who have undergone prostatectomy for prostate cancer	Harbor-UCLA 7-day Sexual Function Questionnaire	Recruiting; estimated primary completion March 2019
Safety, Tolerability, Pharmacokinetic (PK), and Pharmacodynamic Study of GSK 2881078 and Study to Evaluate the Effect of CYP3A4 Inhibition on PK of GSK2881078	NCT02567773	Phase 1	Randomized placebo controlled trial	Part A: GSK2881078 vs Placebo Part B: GSK2881078 + Itraconazole	Part A: Healthy men aged 50–75, post-menopausal women Part B: Healthy men aged 18–60	Measures of tolerability and adverse effects, pharmacokinetic and pharmacodynamic measurements	Completed
Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics Study of GSK2881078 in Single and Repeat Doses	NCT02045940	Phase 1	Randomized placebo controlled crossover assignment	GSK2881078 vs placebo	Healthy males aged 18–50	Safety and tolerability, pharmacokinetics, pharmacodynamics	Completed
A Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of GSK2849466 in Healthy Male Subjects	NCT01696604	Phase 1	Randomized placebo controlled crossover assignment	GSK2849466 vs placebo	Healthy males aged 18–50	Safety and tolerability, pharmacokinetics, pharmacodynamics	Completed

(continued)

Table 1. Continued

Study Title	ClinicalTrials.gov Identifier	Phase	Design	Intervention	Patient Population	Primary Outcome	Status
Study to Evaluate Safety and Tolerability of Single and Multiple Ascending Doses of PF-06260414 in Healthy Western and Japanese Male Subjects	NCT02070939	Phase 1	Randomized placebo controlled	PF-06260414 vs placebo	Healthy males aged 21–50	Safety and tolerability, pharmacokinetics, pharmacodynamics	Completed
GLPG0492 Pharmacodynamics	NCT01538420	Phase 1	Randomized placebo controlled	GLPG0492 vs placebo	Healthy males aged 18–50, post-menopausal women aged 35–65	Safety and tolerability, pharmacokinetics, pharmacodynamics, effect on protein synthesis in muscle	Completed

drug reactions, 2 female subjects developed elevated ALT values 2–2.5 times the upper limit of normal during treatment, and 2 male subjects experienced muscle soreness and elevated creatine kinase levels weeks into the follow-up period.⁵² GSK2881078 was also associated with reductions in HDL.⁵³

PF-06260414, a novel SARM, was also involved in a Phase 1 trial investigating safety, pharmacokinetics, and dynamics.⁵⁴ The study was a combination, randomized, double-blind, placebo-controlled, single- and multiple-dose escalation, parallel-group study in 72 healthy adult men of mixed ethnicity.⁵⁴ Overall PF-06260414 was well tolerated, with the most common AEs being headache and increased serum ALT levels, and decreases in serum HDL levels.⁵⁴ Most other side effects were considered mild (decreased appetite, upper respiratory infection, and dizziness) except for 1 moderate AE of fatigue and 1 severe AE of anxiety that led to drug discontinuation.⁵⁴

LGD-4033, a novel SARM, was tested in a placebo-controlled study of 76 healthy men randomized to either placebo treatment, 0.1 mg, 0.3 mg, or 1.0 mg of LGD-4033 daily for 21 days.⁵⁵ The study assessed the safety, tolerability, pharmacokinetics, and effects of LGD-4033 on LBM, muscle strength, stair-climbing power, and sex hormones.⁵⁵ Overall LGD was well tolerated, and the adverse event frequency was similar between placebo and dosing groups. Expected dose-dependent suppression of testosterone levels and sex hormone binding globulin levels was seen, with a free testosterone level depression seen only in the 1.0 mg group.⁵⁵ LBM increased in a dose-dependent manner, but there was no significant change in fat mass.⁵⁵ HDL levels also fell in a dose-dependent manner, but both lipid and hormone levels returned to baseline after treatment discontinuation.⁵⁵

Thus, clinical testing has shown SARMs to be well tolerated with mild and infrequent AEs. Several of the trials showed no increases in AEs with placebo. The most consistent biologic alteration shared between most of the tested compounds were decreases in HDL levels and transient increases in ALT. Anabolic androgenic steroids (AAS) such as testosterone are known to increase liver transaminase levels, and there have been reports of peliosis hepatis, cholestatic jaundice, and liver malignancies associated with their use.⁵⁶ None of the subjects in the trials mentioned previously had alterations in their bilirubin levels to suggest cholestasis, but several had elevations in ALT, suggesting hepatocellular injury. Liver damage from AAS was initially thought to be caused by an idiosyncratic hypersensitivity reaction, but has been shown to be caused by intrinsic direct hepatotoxicity of AASs depending on individual susceptibility, with genetics playing a role.⁵⁷ Thus, it remains to be seen if SARMs may pose a risk of significant hepatotoxicity and further studies are needed to examine the relationship between these transient ALT elevations and pathologic hepatic changes.

Although HDL is negatively associated with the risk of atherosclerotic disease, pharmacologically induced decreases in serum HDL levels have not necessarily been associated with

changes in cardiovascular risk.⁵⁵ Androgen-induced decreases in serum HDL might be secondary to the upregulation of scavenger receptors involved in HDL metabolism.³⁶ In addition, animal models suggest that the cardioprotective effects of HDL are influenced more by the mechanism of HDL modification rather than changes in HDL levels.³⁶ Thus, evidence would support that androgen-induced changes in serum HDL are not necessarily equivalent to having low HDL at baseline. Considering that SARM administration seems to reduce several cardiac risk factors such as insulin sensitivity and triglycerides, long-term studies are needed to determine the effects of chronic SARM treatment on cardiovascular risk. Efforts are also underway to develop SARMs amenable to transdermal delivery to maximize local concentrations and minimize systemic side effects, such as lowering HDL-C by binding AR in the liver.¹⁹

Potential for Abuse

The anabolic effects of SARMs and their lack of androgenic side effects make them of great interest to the bodybuilding community and create the potential for abuse among competitive athletes.⁴⁹ Unfortunately, despite the lack of FDA approval, many of the SARMs previously mentioned in the studies are available for purchase online, though it is unclear how verifiable their sources are.⁵⁸ Forums complete with starter guides for first-time users (on subjects such as obtaining and interpreting blood work) and links for purchase are easily accessible, and anecdotal experiences and advice are widely shared.⁵⁹ In 2008, the World Anti-doping Agency banned SARMs in sports, citing their potential for abuse.⁴⁹ A study sponsored by governmental anti-doping organizations in Europe used mass spectrometry to identify S-4 (Andarine) and chemically related impurities in supplements being sold online, suggesting that these online retailers are providing biologically active SARMs in their supplements.⁴⁹

CONCLUSION

The AR is a complex signaling apparatus with important effects on tissue development, growth, and maintenance. Although steroid hormones have valuable clinical applications, their widespread activation of AR receptors gives rise to treatment-limiting side effects. Like the SERMs before them, SARMs and their tissue selectivity demonstrate the potential to revolutionize the treatment of many debilitating diseases. Depending on their chemical structure, SARMs can act as agonists, antagonists, partial agonists, or partial antagonists of the AR within different tissues. Results from recent clinical trials have shown mixed but promising results and basic research continues to raise the idea that SARMs could be powerful and effective treatments in a wide variety of conditions, from Alzheimer's disease and osteoporosis to male contraception and BPH.

Continued investigation and development of these agents is called for given their novel mechanisms of action and potential

to address and complement conditions with a lack of effective therapies or therapies with unacceptable side effects. Additionally, to date SARMs have consistently been shown to be well tolerated, easily administered via an oral route, and overall lacking in significant drug interactions that can only further increase their future applicability. Like the SERMs before them, the next decades could herald the approval and widespread use of SARMs for an array of indications. However, further studies are currently needed to determine the safety and efficacy of these medications before they are approved for clinical use.

Corresponding Author: Alexander W. Pastuszak, MD, PhD, Assistant Professor, Division of Urology, Department of Surgery, University of Utah School of Medicine, 30 North 1900 East, Rm #3B420, Salt Lake City, UT 84132, USA. Tel: 713-798-6163; Fax: 713-798-6007; E-mail: alexander.pastuszak@hsc.utah.edu

Conflicts of Interest: The authors report no conflicts of interest.

Funding: A.W.P. is a National Institutes of Health K08 Scholar supported by a Mentored Career Development Award (K08DK115835-01) from the National Institute of Diabetes and Digestive and Kidney Diseases. This work is also supported in part through a Urology Care Foundation Rising Stars in Urology Award (to A.W.P.).

STATEMENT OF AUTHORSHIP

Category 1

(a) Conception and Design

Zachary Solomon, Jorge Rivera Mirabal, Daniel Mazur, Taylor Kohn, Alexander Pastuszak

(b) Acquisition of Data

Zachary Solomon, Jorge Rivera Mirabal

(c) Analysis and Interpretation of Data

Zachary Solomon, Jorge Rivera Mirabal, Daniel Mazur, Taylor Kohn, Larry Lipshultz, Alexander Pastuszak

Category 2

(a) Drafting the Article

Zachary Solomon, Jorge Rivera Mirabal, Daniel Mazur, Taylor Kohn, Alexander Pastuszak

(b) Revising It for Intellectual Content

Zachary Solomon, Jorge Rivera Mirabal, Alexander Pastuszak, Daniel Mazur, Larry Lipshultz

Category 3

(a) Final Approval of the Completed Article

Zachary Solomon, Jorge Rivera Mirabal, Daniel Mazur, Taylor Kohn, Alexander Pastuszak, Larry Lipshultz

REFERENCES

1. Miller CP, Shomali M, Lyttle CR, et al. Design, synthesis, and preclinical characterization of the selective androgen receptor modulator (SARM) RAD140. *ACS Med Chem Lett* 2011; 2:124-129.

2. Crawford J, Prado CMM, Johnston MA, et al. Study design and rationale for the phase 3 clinical development program of enobosarm, a selective androgen receptor modulator, for the prevention and treatment of muscle wasting in cancer patients (POWER Trials). *Curr Oncol Rep* 2016;18:37.
3. Dalton JT, Barnette KG, Bohl CE, et al. The selective androgen receptor modulator GTx-024 (enobosarm) improves lean body mass and physical function in healthy elderly men and postmenopausal women: Results of a double-blind, placebo-controlled phase II trial. *J Cachexia Sarcopenia Muscle* 2011;2:153-161.
4. Unwalla R, Mousseau JJ, Fadeyi OO, et al. Structure-based approach to identify 5-[4-hydroxyphenyl]pyrrole-2-carbonitrile derivatives as potent and tissue selective androgen receptor modulators. *J Med Chem* 2017;60:6451-6457.
5. Jannini EA, Gravina GL, Mortengaler A, et al. Is testosterone a friend or a foe of the prostate? *J Sex Med* 2011;8:946-955.
6. Olea N, Sakabe K, Soto AM, et al. The proliferative effect of "anti-androgens" on the androgen-sensitive human prostate tumor cell line Incap. *Endocrinology* 1990;126:1457-1463.
7. Gravina GL, Marampon F, Sanità P, et al. Episode-like pulse testosterone supplementation induces tumor senescence and growth arrest down-modulating androgen receptor through modulation of p-ERK1/2, pAR^{ser81} and CDK1 signaling: biological implications for men treated with testosterone replacement therapy. *Oncotarget* 2017;8:113792-113806.
8. Handlon AL, Schaller LT, Leesnitzer LM, et al. Optimizing ligand efficiency of selective androgen receptor modulators (SARMs). *ACS Med Chem Lett* 2016;7:83-88.
9. Ponnusamy S, Sullivan RD, You D, et al. Androgen receptor agonists increase lean mass, improve cardiopulmonary functions and extend survival in preclinical models of Duchenne muscular dystrophy. *Hum Mol Genet* 2017;26:2526-2540.
10. Cozzoli A, Capogrosso RF, Sblendorio VT, et al. GLPG0492, a novel selective androgen receptor modulator, improves muscle performance in the exercised-mdx mouse model of muscular dystrophy. *Pharmacol Res* 2013;72:9-24.
11. Chen J, Hwang DJ, Bohl CE, et al. A selective androgen receptor modulator for hormonal male contraception. *J Pharmacol Exp Ther* 2005;312:546-553.
12. Watanabe K, Hirata M, Tominari T, et al. BA321, a novel carborene analog that binds to androgen and estrogen receptors, acts as a new selective androgen receptor modulator of bone in male mice. *Biochem Biophys Res Commun* 2016;478:279-285.
13. Chisamore MJ, Gentile MA, Dillon GM, et al. A novel selective androgen receptor modulator (SARM) MK-4541 exerts anti-androgenic activity in the prostate cancer xenograft R-3327G and anabolic activity on skeletal muscle mass & function in castrated mice. *J Steroid Biochem Mol Biol* 2016;163:88-97.
14. Akita K, Harada K, Ichihara J, et al. A novel selective androgen receptor modulator, NEP28, is efficacious in muscle and brain without serious side effects on prostate. *Eur J Pharmacol* 2013;720:107-114.
15. Zilbermint MF. Nonsteroidal selective androgen receptor modulator Ostarine™ in cancer cachexia. *Futur Oncol* 2009;5:1211-1220.
16. Nejjishima H, Yamamoto N, Suzuki M, et al. Anti-androgenic effects of S-40542, a novel non-steroidal selective androgen receptor modulator (SARM) for the treatment of benign prostatic hyperplasia. *Prostate* 2012;72:1580-1587.
17. Jordan VC. Selective estrogen receptor modulation. *Cancer Res* 2001;61:5683-5687.
18. Chen J. Discovery and therapeutic promise of selective androgen receptor modulators. *Mol Interv* 2005;5:173-188.
19. Saeed A, Vaught GM, Gavardinas K, et al. 2-Chloro-4-[[[1R, 2R]-2-hydroxy-2-methyl-cyclopentyl]amino]-3-methyl-benzonitrile: A transdermal selective androgen receptor modulator (SARM) for muscle atrophy. *J Med Chem* 2016;59:750-755.
20. Hikichi Y, Yamaoka M, Kusaka M, et al. Selective androgen receptor modulator activity of a steroidal antiandrogen TSAA-291 and its cofactor recruitment profile. *Eur J Pharmacol* 2015;765:322-331.
21. Schmidt A, Kimmel DB, Bai C, et al. Discovery of the selective androgen receptor modulator MK-0773 using a rational development strategy based on differential transcriptional requirements for androgenic anabolism versus reproductive physiology. *J Biol Chem* 2010;285:17054-17064.
22. Kohn TP, Louis MR, Pickett SM, et al. Age and duration of testosterone therapy predict time to return of sperm count after human chorionic gonadotropin therapy. *Fertil Steril* 2017;107:351-357.
23. Jones A, Chen J, Hwang DJ, et al. Preclinical characterization of a (S)-N-(4-Cyano-3-trifluoromethyl-phenyl)-3-(3-fluoro, 4-chlorophenoxy)-2-hydroxy-2-methyl-propanamide: A selective androgen receptor modulator for hormonal male contraception. *Endocrinology* 2009;150:385-395.
24. Poutiainen PK, Huhtala T, Jääskeläinen T, et al. Preclinical pharmacology of FL442, a novel nonsteroidal androgen receptor modulator. *Mol Cell Endocrinol* 2014;387:8-18.
25. Schmidt A, Meissner RS, Gentile MA, et al. Identification of an anabolic selective androgen receptor modulator that actively induces death of androgen-independent prostate cancer cells. *J Steroid Biochem Mol Biol* 2014;143:29-39.
26. Yang J, Wu Z, Wu D, et al. Pharmacokinetics, biodistribution and metabolism of a novel selective androgen receptor modulator designed for prostate cancer imaging. *Int J Oncol* 2010;36:213-222.
27. Vignozzi L, Corona G, Petrone L, et al. Testosterone and sexual activity. *J Endocrinol Invest* 2005;28:39-44.
28. Simon JA, Goldstein I, Kim NN, et al. The role of androgens in the treatment of genitourinary syndrome of menopause (GSM): International Society for the Study of Women's Sexual Health (ISSWSH) expert consensus panel review. *Menopause* 2018;25:837-847.
29. Traish AM, Vignozzi L, Simon JA, et al. Role of androgens in female genitourinary tissue structure and function: Implications in the genitourinary syndrome of menopause. *Sex Med Rev* 2018;6:558-571.

30. Labrie F, Derogatis L, Archer DF, et al. Effect of intravaginal prasterone on sexual dysfunction in postmenopausal women with vulvovaginal atrophy. *J Sex Med* 2015;12:2401-2412.
31. Jones A, Hwang DJ, Duke CB, et al. Nonsteroidal selective androgen receptor modulators enhance female sexual motivation. *J Pharmacol Exp Ther* 2010;334:439-448.
32. Simon J, Braunstein G, Nachtigall L, et al. Testosterone patch increases sexual activity and desire in surgically menopausal women with hypoactive sexual desire disorder. *J Clin Endocrinol Metab* 2005;90:5226-5233.
33. Wang C, Cunningham G, Dobs A, et al. Long-term testosterone gel (AndroGel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone mineral density in hypogonadal men. *J Clin Endocrinol Metab* 2004;89:2085-2098.
34. Miner JN, Chang W, Chapman MS, et al. An orally active selective androgen receptor modulator is efficacious on bone, muscle, and sex function with reduced impact on prostate. *Endocrinology* 2007;148:363-373.
35. Vignozzi L, Cellai I, Santi R, et al. Antiinflammatory effect of androgen receptor activation in human benign prostatic hyperplasia cells. *J Endocrinol* 2012;214:31-43.
36. Vignozzi L, Morelli A, Sarchielli E, et al. Testosterone protects from metabolic syndrome-associated prostate inflammation: An experimental study in rabbit. *J Endocrinol* 2012;212:71-84.
37. Miller DD, Dalton JT. Comparison of the pharmacological effects of a novel selective androgen receptor modulator, the 5-hydroxyflutamide in intact rats. *New approach for benign prostate hyperplasia* 2004;145:5420-5428.
38. Holland J, Bandelow S, Hogervorst E. Testosterone levels and cognition in elderly men: A review. *Maturitas* 2011;69:322-327.
39. Ciocca G, Limoncin E, Carosa E, et al. Is testosterone a food for the brain? *Sex Med Rev* 2016;4:15-25.
40. Burkhardt MS, Foster JK, Clarnette RM, et al. Interaction between testosterone and apolipoprotein E epsilon4 status on cognition in healthy older men. *J Clin Endocrinol Metab* 2006;91:1168-1172.
41. Moffat SD, Zonderman AB, Metter EJ, et al. Longitudinal assessment of serum free testosterone concentration predicts memory performance and cognitive status in elderly men. *J Clin Endocrinol Metab* 2002;87:5001-5007.
42. Jones A, Hwang D-J, Narayanan R, et al. Effects of a novel selective androgen receptor modulator on dexamethasone-induced and hypogonadism-induced muscle atrophy. *Endocrinology* 2010;151:3706-3719.
43. Shankaran M, Shearer TW, Stimpson SA, et al. Proteome-wide muscle protein fractional synthesis rates predict muscle mass gain in response to a selective androgen receptor modulator in rats. *Am J Physiol Endocrinol Metab* 2015;310:E405-417.
44. Dubois V, Simitsidellis I, Laurent MR, et al. Enobosarm (GTx-024) modulates adult skeletal muscle mass independently of the androgen receptor in the satellite cell lineage. *Endocrinology* 2015;156:4522-4533.
45. Blanqué R, Lepescheux L, Auberval M, et al. Characterization of GLPG0492, a selective androgen receptor modulator, in a mouse model of hindlimb immobilization. *BMC Musculoskelet Disord* 2014;15:291.
46. Narayanan R, Dalton JT. Androgen receptor: A complex therapeutic target for breast cancer. *Cancers (Basel)* 2016;8:1-17.
47. Vontela N, Koduri V, Schwartzberg LS, et al. Selective androgen receptor modulator in a patient with hormone-positive metastatic breast cancer. *J Natl Compr Canc Netw* 2017;15:284-287.
48. Pembrolizumab and enobosarm in treating patients with androgen receptor positive metastatic triple negative breast cancer. Available at <https://clinicaltrials.gov/ct2/show/NCT02971761>. Accessed October 20, 2017.
49. Thevis M. Detection of the arylpropionamide-derived selective androgen receptor modulator (SARM) S-4 (Andarine) in a black-market product. *Drug Test Anal* 2009;1:387-392.
50. Dobs AS, Boccia RV, Croot CC, et al. Effects of enobosarm on muscle wasting and physical function in patients with cancer: A double-blind, randomised controlled phase 2 trial. *Lancet Oncol* 2013;14:335-345.
51. GTx reports results for enobosarm POWER trials for the prevention and treatment of muscle wasting in patients with non-small cell lung cancer. Available at: <http://www.businesswire.com/news/home/20130819005378/en/GTx-Reports-Results-Enobosarm-POWER-Trials-Prevention>. Accessed October 21, 2017.
52. Thirumalai A, Berkseth KE, Amory JK. Treatment of hypogonadism: Current and future therapies. *F1000Research* 2017;6:68. <https://doi.org/10.12688/f1000research.10102.1>.
53. Clark RV, Walker AC, Andrews S, et al. Safety, pharmacokinetics and pharmacological effects of the selective androgen receptor modulator, GSK2881078, in healthy men and postmenopausal women. *Br J Clin Pharmacol* 2017:1-16.
54. Bhattacharya I, Tarabar S, Liang Y, et al. Safety, pharmacokinetic, and pharmacodynamic evaluation after single and multiple ascending doses of a novel selective androgen receptor modulator in healthy subjects. *Clin Ther* 2016;38:1401-1416.
55. Basaria S, Collins L, Dillon EL, et al. The safety, pharmacokinetics, and effects of LGD-4033, a novel nonsteroidal oral, selective androgen receptor modulator, in healthy young men. *Journals Gerontol - Ser A Biol Sci Med Sci* 2013;68:87-95.
56. Wu C, Kovac JR. Novel uses for the anabolic androgenic steroids nandrolone and oxandrolone in the management of male health. *Curr Urol Rep* 2016;17:1-7.
57. Stimac D, Milić S, Dintinjana RD, et al. Androgenic/anabolic steroid-induced toxic hepatitis. *J Clin Gastroenterol* 2002;35:350-352.
58. Best place to buy SARMS online - Quality SARMS for sale. Available at: <https://sarmspharm.com/>. Accessed October 20, 2017.
59. iSARMS.com. Available at: <https://www.isarms.com/>. Accessed October 20, 2017.