Androgens are essential for male development and the maintenance of male secondary characteristics, such as bone mass, muscle mass, body composition, and spermatogenesis. The main disadvantages of steroidal androgens are their undesirable physicochemical and pharmacokinetic properties. The recent discovery of nonsteroidal selective androgen receptor modulators (SARMs) provides a promising alternative for testosterone replacement therapies with advantages including oral bioavailability, flexibility of structural modification, androgen receptor specificity, tissue selectivity, and the lack of steroid-related side effects.
Review

Introduction

The beneficial effects of testosterone on muscle, bone, and physique have been known for over a century. Yet testosterone and its esters are approved for only a limited number of therapeutic applications, including primary or hypogonadal hypogonadism and delayed puberty. Testosterone and structurally-related analogs, steroids have been denoted to the therapy of final resort for anemia, endometriosis, and metastatic breast cancer owing to the recent development and widespread clinical use of more effective therapies (e.g., erythropoietin, aromatase inhibitors, and TNFα inhibitors). Recent interest in using testosterone as hormone replacement in aging men or in age-related frailty has been slowed because of widespread concerns related to the effects of testosterone on the prostate, serum lipids, and cardiovascular system. The discovery and clinical development of selective estrogen receptor modulators (SERMs) transformed the therapeutic use of estrogen. Nonsteroidal selective androgen receptor modulators (SARMs) with the ability to selectively stimulate or maintain muscle and bone mass with lesser pharmacologic effects in the prostate are now leading a similar revolution in the therapeutic use of androgens.

Action of Androgens on Target Tissues

The overall physiological effects of endogenous androgens are contributed by testosterone and its active metabolites, dihydrotestosterone (DHT) and estradiol. Approximately 6 to 8% of testosterone is converted to DHT through the action of type 2 5α-reductase, an enzyme highly expressed in male accessory sex organs, hair follicles, and genital skin. Approximately 0.3% of testosterone is converted to estradiol via the action of aromatase, an enzyme expressed in the brain, liver, and adipose tissue (1). Testosterone and DHT execute their actions predominantly through the androgen receptor (AR), which belongs to the nuclear receptor superfamily and functions as a ligand-dependent transcription factor. More than 95% of circulating testosterone is synthesized and secreted by the Leydig cells in the testes. Circulating testosterone is essential for the differentiation and growth of male accessory reproductive organs (e.g., prostate and seminal vesicles), control of male sexual behavior, and the development and maintenance of male secondary characteristics that involve muscle, bone, larynx, and hair (2). For decades, androgens have been primarily used for hormonal replacement in hypogonadal men. Whereas severe hypogonadism is uncommon, disease and aging-related androgen insufficiency is much more frequent. Low endogenous testosterone concentrations are associated with osteoporosis and frailty arising from decreased fat-free mass, lowered muscle strength, and reduced bone mineral density (BMD). Recently, multiple clinical trials of hormone replacement using testosterone were conducted in aging men (for review, see [2]). The potential benefits of testosterone replacement therapy include increase in BMD, improvement in body composition and strength, sexual function, cognitive function, and mood, however, the potential risks of such treatments, including those in the cardiovascular system, blood (e.g., hematocrit and hemoglobin levels), and prostate are routinely experienced. Large-scale and long-term clinical trials are needed to evaluate the risk–benefit ratio of testosterone replacement therapy in aging men. Another important line of research using testosterone is hormonally-mediated male contraception (reviewed to below, for brevity’s sake, as hormonal male contraception). A variety of attempts have been made to produce pharmacologic, effective, reversible and side-effect-free contraceptive methods for the male. Hormonal male contraception has only recently reached the stage of clinical development (for review, see [3]).

Spermatogenesis

Circulating testosterone participates in the regulation of androgen production by the hypothalamus-pituitary-testes axis. As illustrated in Figure 1, gonadotropin-releasing hormone (GnRH) is released from the hypothalamus and stimulates the pulsatile secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary. LH and FSH, in turn, stimulate testicular androgen synthesis and release testosterone synthesized by Leydig cells, while FSH directly interacts with FSH receptors expressed in Sertoli cells and stimulates spermatogenesis through testosterone synthesized by Leydig cells, while FSH directly interacts with FSH receptors expressed in Sertoli cells and stimulates spermatogenesis. Testosterone and its aromatized metabolite (estradiol) negatively regulate circulating levels of testosterone in the hypothalamus and pituitary. Androgen and estrogen produced by Leydig cells stimulate or inhibit, respectively, the secretion of FSH from the pituitary (4). High concentrations of intratubular testosterone are essential for the initiation and maintenance of spermatogenesis as evidenced by the infertility of hypogonadal men. Results from both animal models and man, however, support the requirement for both FSH and testosterone in achieving quantitative and qualitative spermatogenesis (for review, see [5]).

Bone

Bone is a living tissue, which is continually being broken down (i.e., bone resorption) and regenerated (i.e., bone formation) by osteoclasts and osteoblasts, respectively. AR ligands affect BMD by directly interacting with FSH receptors expressed in Sertoli cells and stimulating spermatogenesis. Testosterone and its aromatized metabolite (estradiol) negatively regulate circulating levels of testosterone in the hypothalamus and pituitary. Androgen and estrogen produced by Leydig cells stimulate or inhibit, respectively, the secretion of FSH from the pituitary (4). High concentrations of intratubular testosterone are essential for the initiation and maintenance of spermatogenesis as evidenced by the infertility of hypogonadal men. Results from both animal models and man, however, support the requirement for both FSH and testosterone in achieving quantitative and qualitative spermatogenesis (for review, see [5]).
androgens have a stimulatory effect on expression of alkaline phosphatase, type I collagen, and osteocalcin, and increased mineralization of the extracellular bone matrix (9). Moreover, DHT has a suppressive effect on osteoclast differentiation (10).

Muscle

The mechanism of androgen action on muscle remains largely unknown. The common hypothesis is that androgens promote muscle protein synthesis. There is evidence to support the idea that testosterone supplementation increases muscle protein synthesis in elderly men (11) and young hypogonadal men (12). Also, androgen-induced increases in muscle mass appear to arise from muscle fiber hypertrophy rather than hyperplasia (i.e., cellular enlargement rather than cellular proliferation) (13). Androgen increases cross-sectional areas of both type I and type II muscle fibers in a dose-dependent manner, but does not alter the absolute number or the ratio of type I and type II fibers. Androgen-induced increases in muscle fiber cross-sectional area were correlated with the increase in myonuclear number and satellite cell number. These findings suggest that androgen increases satellite cell number, resulting in muscle fiber hypertrophy and myonuclear number increase. The molecular mechanisms of the androgenic effect on satellite cell numbers are not well understood. Taylor et al. reported that androgen stimulates the differentiation of mesenchymal pluripotent...
cells to the myogenic lineage (14); however, other possible pathways, including increases in satellite cell proliferation and decreases in satellite cell apoptosis are possible but remain unknown.

**Prostate**

In the prostate, testosterone is rapidly converted to DHT by type 2 5α-reductase. Conversion to DHT amplifies the action of testosterone by 3–5-fold, owing to the greater binding affinity of DHT (as compared to testosterone) to the AR (15). DHT plays a critical role in determining prostate size prior to and during adulthood and is believed to be essential for the development of benign prostatic hyperplasia (BPH), which occurs in 50% and 90% of men in their fifties and nineties, respectively, in the United States. The major problem associated with BPH is lower urinary tract symptoms (LUTS). Multiple lines of evidence suggest the importance of androgen, especially DHT, in the development of BPH. For instance, BPH does not develop in males with certain type 2 5α-reductase mutations or in males with very low levels of androgen due to prepubertal castration or hypopituitarism-related hypogonadism (16). Moreover, clinical treatment of BPH either by chemical or surgical castration, or with a type 2 5α-reductase inhibitor (e.g., finasteride) induces apoptosis of epithelial cells, which in turn significantly decreases the volume of the prostate (17). Recently, the role of age-dependent changes in the intraprostatic hormonal environment in the development of BPH was evaluated. Despite the aging-related decrease in testosterone and intraprostatic DHT production, an increased estradiol–DHT ratio was found in the transition zone of aging human prostate. This relative estrogen-dominant status was believed to be relevant to the development of BPH (18). Furthermore, estradiol is capable of inducing precancerous lesions and prostate cancer in aging dogs (19). Therefore, testosterone supplementation in older men raises concern with regard to acceleration of BPH and/or prostate cancer.

**Limitations of Steroidal Androgens**

Since the discovery of the therapeutic benefits of testosterone in the 1930s, a variety of androgen preparations have been introduced and used clinically. Unfortunately, virtually all of the current available androgen preparations have severe limitations (20). Unmodified testosterone demonstrates little pharmacologic activity after oral administration resulting from its rapid hepatic elimination. To prolong pharmacologic effects, testosterone implants and longer acting esters, including testosterone enanthate (TE), testosterone propionate (TP), testosterone buciclate (TB), testosterone undecanoate (TU), and testosterone decanoate (TD), were developed. Except for TU, the administration routes of most testosterone esters are limited to intramuscular injection (im), surgical implantation for implants and pellets, or transdermal delivery, such as patches and gels. Furthermore, serum testosterone levels fluctuate greatly between injections, and skin rashes and irritation are associated with testosterone patches. The other major limitations for using steroidal androgens for hormonal male contraception, which requires high

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<th>Chemotype</th>
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<th>ID of Lead Molecules</th>
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<td>Ostarine</td>
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* Information about stage of development was obtained through company websites. BMS, Bristol-Myers Squibb.
doses of androgen, are steroid-related side effects, including decrease of HDL cholesterol, increase of homocysteine parameters such as hemoglobin and hematocrit, increased body weight, and acne (3). To use testosterone for potential long-term hormone replacement in aging men, the potential risk in the prostate and cardiovascular system needs to be evaluated carefully by large prospective clinical trials.

**Pharmacophores and Molecular Mechanism of SARMs**

The recent and successful marketing and clinical application of selective estrogen receptor modulators (SERMs) stimulated a great interest in the discovery and development of nonsteroidal selective androgen receptor modulators (SARMs). Progress has been made in identifying novel pharmacophores of nonsteroidal SARMs by structural modification of nonsteroidal antiandrogens. As listed in Table 1, SARM pharmacophores can be classified into four categories: aryl-propionamide, bicyclic hydantoin, quinoline, and tetrahydroquinoline analogs. One uniform characteristic of these compounds is that they are not substrates for aromatase or 5α-reductase. These nonsteroidal AR ligands are known to act as full agonists in androgenic organs (e.g., muscle and bone) but as partial agonists in androgenic tissues (e.g., prostate and seminal vesicles). Additionally, some SARMs have more favorable pharmacokinetic properties. AR receptor specificity, and are more amenable to structural modifications than their steroidal counterparts. SARMs may therefore be of benefit for the treatment of primary or secondary hypogonadism, osteopenia or osteoporosis, frailty, acquired immunodeficiency syndrome (AIDS) or cancer-related cachexia, rehabilitation, anemias, BPH, and hormonal male contraception.

General molecular mechanisms of tissue-selective nuclear receptor modulators were proposed recently to facilitate understanding of nuclear receptor pharmacology (21). Within the nuclear receptor superfamily, molecular mechanisms of SARMs are best understood. The tissue selective action of SARMs is mainly based on the differential expression of two types of estrogen receptor (ER) in target tissues and consequently the differential ligand-ER conformation, the promoter context of the target genes, and recruitment and availability of coregulator proteins (22). In contrast to the ER, a single form of the AR is ubiquitously expressed throughout the body. Notably, testosterone is locally metabolized to DHT by type 2 5α-reductase, which is highly expressed in the prostate and other genital tissues but not in anabolic organs, such as muscle and bone. DHT is a more potent androgen than testosterone and is believed to amplify the androgenic activity of testosterone in some tissues. Administration of finasteride, a 5α-reductase inhibitor, to intact male rats significantly decreases the prostate mass. Additionally, administration of testosterone with a 5α-reductase inhibitor in castrated rats attenuated the androgenic activity of testosterone in the prostate (23). As with SERMs, which are not substrates for 5α-reductase, the tissue selectivities of testosterone and DHT arise from, at least partially, the lack of such active metabolic amplification in androgenic organs. Other possible molecular mechanisms related to the tissue selectivity of SARMs include ligand-dependent changes in AR conformation, differential interaction with the promoter context of target genes, and differential recruitment of coregulators in target tissues. The discovery of SARMs not only provides a potentially significant therapeutic advance for androgen replacement therapy, but also provides model compounds to further study the molecular mechanism of action of the AR.

**Outline of Drug Discovery of Aryl-Propionamide SARMs**

Nonsteroidal AR agonists (i.e., androgens) were recently reported by our laboratories as well as others (24–27). Compounds that demonstrated higher anabolic activity than androgenic activity in vivo were identified as selective androgen receptor modulators (SARMs). The ultimate goal of research in this field is to discover chemical compounds that can be used for androgen replacement therapy to address one or some functions of prototypic steroidal androgens without unwanted side-effects. Treatment should be tailored to the specific need of patients with the best desirable pharmacologic activity. Although a variety of pharmacophores and lead molecules are being developed for clinical use (Table 1), the majority of published preclinical research to date focuses on a series of aryl-propionamide analogs first reported in 1998 (24). Information regarding the state-of-the-art drug discovery of the aryl-propionamide SARMs is given in the sections below.

**In Vitro and In Vivo Structure-Activity Relationships of Nonsteroidal AR Ligands**

Early structure-activity relationship (SAR) work on hydroxyflutamide analogs (28) confirmed the importance of an electron-deficient aromatic ring and of the substituents attached to the carbon atom
Review

Two years later, Tucker et al. (29) reported that the AR binding and antiandrogenic activity of hydroxy-flutamide and bicalutamide (Figure 2) derivatives were optimum when the 4-position substituent in the A-ring was either a cyano or nitro group and the 3-position substituent was a chloro or trifluoromethyl group. It's interesting to note that partial androgen agonist activity was observed in some trifluoromethyl-substituted compounds, suggesting that AR agonists could be designed and developed by subtle structural modification(s) of known AR antagonists.

When the idea of trifluoromethylation was utilized by our laboratory to discover novel aryl-propionamide AR agonists, we identified novel and important in vitro SARs for the AR-binding affinity and agonist activity (30, 31), including a para-nitro group in the A-ring, a trifluoromethyl group linked to the chiral carbon (R-isomer), a thin-ether linkage, and a halo or para-N-allylamide group in the B-ring. When these compounds were tested in vitro, however, no pharmacologic activity was observed owing to their unfavorable pharmacokinetic properties (32). Further structural modification was made to overcome this problem by changing the thin-ether linkage to an ether, which resulted in the successful discovery of the first member, S-4, of a new series of SARMs (33, 34).

As shown in Figure 3, S-4 acted as a full AR agonist in the levator ani muscle, as indicated its ability to fully maintain the muscle to that of control level. However, S-4 acted as a partial agonist in the prostate (Emax = 35% of control values), indicating that S-4 was potent and efficacious in anabolic tissues but not in androgenic tissues. In contrast, castrated rats treated with testosterone propionate had near identical, and non-selective growth of the prostate and levator ani muscle as compared to control animals. Moreover, a variety of structural modifications of known SARMs were made to further explore SARs of nonsteroidal AR ligands (Figure 2) and discover novel SARMs having efficacious and potent in vitro pharmacologic activity and favorable pharmacokinetic properties.

For type I SARMs, in vitro AR binding affinity decreased as the size of the halogen atom increased and/or electronegativity decreased (35). In contrast, a chloro-substituted SARM (i.e., S-9) demonstrated the highest in vivo pharmacologic activity. Further pharmacokinetics studies revealed that the terminal half-life of these SARMs ranged from 4.1 to 14.7 hours in the rat and increased as the size of the halogen atom increased. These studies suggested that high efficacy and potency of SARMs should be predicted by two factors, namely high binding affinity (i.e., Ki < 10 nM) and low in vivo clearance (35). For type II SARMs, the para and meta positions of the B-ring are the optimum positions to introduce small size electron-withdrawing moieties, such as fluoro, chloro, nitro, or cyano groups. The incorporation of a meta-fluoro group in the B-ring of S-9 (to become the novel SARM C-6) resulted in further improved pharmacologic activity in the rat and potential feasibility for hormonal male contraception (36).

Figure 3. Tissue-selective pharmacologic activity of S-4. A. Male rats were castrated and treated for 14 consecutive days with S-4. S-4 potently stimulates muscle growth, but is unable to maintain prostate size. Adapted from J. Pharmacol. Exp. Therap. 304, 1334 (2005).

B. Testosterone stimulates muscle and prostate growth to the same extent.

beating a tertiary hydroxyl group. Two years later, Tucker et al. (29) reported that the AR binding and antiandrogenic activity of hydroxy-flutamide and bicalutamide (Figure 2) derivatives were optimum when the 4-position substituent in the A-ring was either a cyano or nitro group and the 3-position substituent was a chloro or trifluoromethyl group. It’s interesting to note that partial androgen agonist activity was observed in some trifluoromethyl-substituted compounds, suggesting that AR agonists could be designed and developed by subtle structural modification(s) of known AR antagonists.

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Figure 3. Tissue-selective pharmacologic activity of S-4. A. Male rats were castrated and treated for 14 consecutive days with S-4. S-4 potently stimulates muscle growth, but is unable to maintain prostate size. Adapted from J. Pharmacol. Exp. Therap. 304, 1334 (2005).

B. Testosterone stimulates muscle and prostate growth to the same extent.
Unlike the aromatic B-ring, the Ar of our SARM pharmacophore is more restricted in terms of possible structural modifications. Heterocyclic A-ring derivatives failed to retain AR binding affinity (i.e., $K_i > 700 \text{ nM}$), which probably arose from steric hindrance upon binding with the AR. For type III SARMs, compounds with a para-cyano group and a meta-halogen group in the A ring maintained high AR binding affinity and in vivo pharmacologic activity in the rat (37).

**Pharmacokinetics and Metabolism of SARMs**

A series of AR ligands (e.g., acetothiolutamide) studied by Yin et al. exhibited similar AR binding affinity as that of testosterone and high in vitro functional activity; however, these compounds were inactive in the rat owing to rapid hepatic elimination ($t_{1/2} = 26 \text{ min}$) (32). Three major metabolism pathways of acetothiolutamide were identified, including oxidation of the thio-ether linkage, hydrolysis of the amide bond linked to the B-ring, and sulfoxide conjugation. Replacing the thio-ether linkage of acetothiolutamide significantly decreased the rate of hepatic metabolism and permitted identification of the first member of this series of SARMs, S-4. In the rat, S-4 exhibited linear pharmacokinetics within the pharmacologic dose range after iv administration (38). The lack of parent drug in the urine suggests that S-4 is extensively metabolized. Both in vitro and in vivo metabolism studies showed that S-4 is deacetylated in rats, dogs, and humans (39). The average terminal half-life of S-4 in the rat and dog was approximately four hours. After oral dosing, S-4 was rapidly absorbed and completely bioavailable. We replaced the acetamido group in the A ring with different halogen groups to examine its role in pharmacologic activity. As discussed in the SAR section, these structural modifications significantly altered the in vivo pharmacologic activity of these SARM by changing their AR binding affinity and pharmacokinetic properties. It is worth noting that SARMs with high AR binding affinity (i.e., $K_i < 10 \text{ nM}$) exerted nearly identical in vivo pharmacokinetic properties. It is worth noting that SARMs with high AR binding affinity were inactive in the rat owing to rapid hepatic elimination ($t_{1/2} = 26 \text{ min}$) (32).

**Crystallography and Molecular Modeling of SARMs**

To facilitate the rational design of novel and more potent SARMs, three-dimensional models for the human AR ligand binding domain (LBD) bound to testosterone have been developed based on the crystal structure of the highly homologous human progesterone receptor LBD (42). Moreover, the binding modes of several hydroxyfutamide-derived AR ligands were investigated using flexible docking with FlexX, a computer program for predicting protein-ligand interactions. In this work, Maribella et al. proposed that a unique unoccupied subpocket existed within the AR binding pocket, which may be valuable for ligand optimization of nonsteroidal AR ligands and discovery of novel SARMs. Recently, we examined the three-dimensional quantitative structure-activity relationship (QSAR) of a group of endogenous androgens and nonsteroidal AR ligands for the AR using comparative molecular field analysis (CoMFA) (43). In this work, the homology model of the AR developed by Maribella et al. was used as a scaffold. The integrated homology modeling, and CoMFA studies identified key amino acids thought to directly interact with our SARMs. According to these studies, the B-ring was positioned in a subpocket bordered by Met486, Cys490, and Met491. More recently, the crystal structure of the AR mutant W741L LBD bound to R-bicalutamide at 1.8 Å resolution was solved (49). This mutation confers agonist activity to bicalutamide and may facilitate understanding of the binding modes of bicalutamide-derived nonsteroidal AR ligands. Positions of AR residues and the majority of ligand binding plane were similar between the mutant AR W741L-bicalutamide LBD complex and wild-type AR-DHT LBD complex (49). However, the absence of the W741 side-chain in the mutant AR W741L allows the 8-ring of R-bicalutamide to be accommodated within a region not occupied by DHT and to make direct contact with residues of helix H12. It was proposed by Ibi et al. that the binding modes of AR bound with the aryl-propionamide SARM pharmacophore would be similar to that observed in AR mutant W741L LBD bound to R-bicalutamide. Ongoing crystallography studies in our laboratory focus on the binding modes of SARMs and R-bicalutamide in the wild-type AR LBD and full-length AR. Molecular modeling based on the crystal structure of AR–SARM LBD complex should be more useful and accurate than using homology AR models in the design of novel AR ligands and prediction of binding affinity and/or functional activity of novel nonsteroidal AR ligands. In summary, in vitro and in vivo SAR studies show that the aromatic B-ring of the aryl-propionamide SARM pharmacophore is amenable to structural modifications and critical for pharmacologic activity. Although the majority of arylpropionamide derivatives demonstrated high oral bioavailability in the rat, the other pharmacokinetic properties (e.g., volume of distribution and clearance) varied significantly in vivo. In vitro AR binding affinity, intrinsic activity of the ligand, and in vivo drug exposure contribute to the overall in vivo potency and efficacy of SARMs. Molecular modeling of nonsteroidal AR ligands is used commonly in conjunction with pharmacology, pharmacodynamics, pharmacokinetics, and
metabolism, to examine and predict the best structural properties. Enhanced understanding of the molecular interactions between non-
steroidal ligand and the AR has advanced significantly in the last five years and, with time, will lead to further structural optimization and
discovery and development of SARMs.

**Therapeutic Promise of SARMs**

**General**

SARMs are currently in the early stages of development, meaning
that only animal data is available and that limited endpoint mark-
bets have been studied. Nevertheless, the development of SARMs
for clinical uses is promising based on preclinical data. Owing to
their selectively high anabolic activity, SARMs could be used for
prevention or treatment of many diseases, including muscle wasting,
cancerous, frailty, or other conditions associated with aging or
androgen deficiency—without unwanted side effects associated with
testosterone. In addition, SARMs that act as partial agonists in
the prostate could be used to prevent or treat BPH. Likewise, SARMs
might be used for hormonal male contraception. In contrast to the
overall pharmacologic activity of testosterone, which arises from
testosterone, DHT, and estradiol, SARMs lack estrogenic-like activity
and do not demonstrate amplified activity in the prostate. Estrogen
is important in bone development and its effects might be related
to cognitive function, libido, and cardiovascular function in the male.
It is still unknown whether SARMs alone will cover the full
spectrum of beneficial effects provided by testosterone replacement
or not. Near-term phase II and III clinical trials of SARMs should
provide insight to their potential therapeutic use.

**Treatment of Muscle Wasting**

Testosterone replacement in young hypogonadal men as a physi-
ologic dose is associated with changes in body composition (i.e.,
gain of lean mass and loss of fat mass) and increase in muscle pro-
tensity (42, 46). Moreover, administration of testosterone at
a physiologic dose increases maximal voluntary strength in young
hypogonadal men (46). Administration of a supraphysiologic dose
of testosterone (above six times the dose needed to achieve normal
serum concentrations) to healthy normal men increases fat-free mass
to a similar extent as resistance-exercise training. The combinational
therapy of resistance exercise and a supraphysiologic dose of testos-
terone showed additive effects on fat-free mass and muscle size and
strength. Similarly, administration of a supraphysiologic dose of tes-
tosterone is associated with increase in maximal voluntary strength
and quadriceps cross-sectional area and volume (47).

The majority of studies to date examined the effects of testos-
terone replacement in older men. Generally, testosterone replace-
ment in elderly men produced modest increases in muscle mass and
strength. Some studies reported modest increases in lean mass (i.e.,
whole body mass excluding bone and fat mass) (46). Few studies,
however, have reported that androgen replacement increases grip
strength (49); in fact, at least one has shown that it does not (50).
Likewise, the effects of testosterone administration on lower-body
strength were not significant in several studies (48). Although the
effect of testosterone on muscle mass and strength in elderly men
has not been consistent or impressive, these results do not suggest
that the administration of SARMs would not be beneficial in terms
of muscle mass and strength in elderly men. Only lower doses of
testosterone were considered for studies in elderly men, owing to
the concerns of side effects at higher doses, especially accelerating
the risk of prostate cancer. A study showed that administration of
testosterone at 125, 300, or 600 mg/week significantly increased
muscle mass and strength equally in older and younger men. These
actions of androgen in muscle seem to have a dose (and concentra-
tion)-dependent relationship (51). In healthy young men, testosterone
dose and testosterone concentrations, including total, free, and
steady-state concentration, were highly correlated. Also, there were
positive correlations between the testosterone dose administered
and gains in fat-free mass, leg press strength, and leg power whereas
testosterone dose and fat mass were inversely correlated. Moreover,
preoperative administration of supraphysiologic doses of testoster-
one tended to shorten hospital stay and improve walking and stair
climbing in older men undergoing knee replacement surgery. In postoperative day 3, there was a significant improvement in the tes-
tosterone treatment group in the ability to stand (52).

It would seem that aromatization of androgens to estrogen is
not required for mediating their anabolic effects on muscle. Both
testosterone and non-aromaticable androgen (i.e., nandrolone)
increased muscle mass and strength, and there was no significant
difference between testosterone and nandrolone in the magnitude of
increase in muscle (53). Also, males with a dysfunction of estrogen
action have normal muscle phenotypes.

SARMs demonstrate strong agonistic activity and an ability to
promote growth of the levator ani muscle, maximally to a size sig-
nificantly greater than that of intact control animals (54). However,
the anabolic activity of SARMs in the levator ani muscle does not
directly support the contention that SARMs will improve muscle
performance. Recently, the effects of S-4 on the mass and strength
of skeletal muscle (isolated soleus muscle) in orchidectomized
rats were measured (55). S-4 treatment (3 mg/kg and 10 mg/kg)
significantly increased the skeletal muscle strength (measured as
peak isometric tension) in orchidectomized animals, even though the
effect of S-4 in muscle size was not significant. S-4 restored castra-
tion-induced losses in lean body mass. Similar changes in muscle
size, muscle strength, and lean body mass were also observed in
DHT-reated (3 mg/kg) animals. However, DHT (3 mg/kg) also fully
restored the androgenic tissue weights, whereas S-4 (3 mg/kg) only
restored the prostate and seminal vesicle to 16% and 17%, respec-
tively, of the control levels.

In summary, administration of androgen significantly increases
muscle mass and strength in young hypogonadal men (physiologic
replacement dose) and eugonadal men (supraphysiologic dose). In
elderly men, testosterone effects on muscle mass and strength have

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not been consistent or impressive, possibly due to the low dosages used in clinical trials. The high correlation between dose (and concentration) and the anabolic actions of androgen in muscle suggests that androgen administration of higher doses in elderly men may significantly increase muscle mass and strength. The aromatization of androgens to estrogen is not required for mediating their anabolic effects on the muscle, suggesting that SARMs can also increase muscle mass and strength. In orchidectomized animals, S-4 showed strong anabolic effects in skeletal muscle without affecting the androgenic tissues. This evidence strongly supports the great potential of SARMs as anabolic agents to treat muscle wasting, improve muscle performance in the frail, and shorten rehabilitation time after surgery.

Prevention and Treatment of Osteoporosis

Numerous lines of evidence indicate that androgens are important in bone, and that SARMs may represent a novel approach to treat-ment of osteoporosis. Reduction of androgen concentration corre-sponds to bone and that SARMs may represent a novel approach to treat-ment of osteoporosis. Prevention and Treatment of Osteoporosis. SARMs significantly increased BMD and bone strength in orchidectomized rat. This observation suggests that a SARM might increase BMD by direct anabolic action and indirect action through muscle stimulation, even though this comparison was performed in different bones.

In conclusion, SARMs are still in the early stages of drug develop-ment and knowledge of their activity in the skeleton remains sparse; nonetheless, SARMs have great potential for treatment of osteoporosis. First, their unique tissue selectivity might make for the beneficial usage of AR ligands as a treatment of osteoporosis. SARMs can minimize undesirable side effects, resulting from stimulation of androgenic organs and cross-reactivity of androgens and their metabolites. Moreover, the anabolic effect of SARMs in bone could...
likely be promoted by higher dosage regimen than conventional dos- 
age for medical androgen. Because conventional medical androgen 
dosages are restricted by side effects, second, SARMs promote bone 
formation, rather than reduce resorptive action, which suggest that 
SARMs can restore bone mass even for severe osteoporosis as well as 
preventive and early stage osteoporosis. Combination therapy with 
other anti-resorptive agents might synergistically increase bone mass 
and strength. Finally, the anabolic effects of androgen on muscle 
are beneficial for increasing bone mass and reducing fracture risk.

The pharmacokinetic advantages, selectivity, and dual activity of 
SARMs in muscle and bone suggest that they may indeed become 
an important new addition to the armamentarium of drugs to treat 
osteoporosis.

Hormonal Male Contraception

Unlike female contraceptive measures, effective male contraception 
is restricted to physical methods, namely condoms and vasectomy. 
A variety of attempts have been made to produce pharmacologic, 
effective, reversible and side effects–free contraceptive methods for 
the male. Among them, only hormonally-based contraception has 
reached the stage of clinical development. Theoretically, inhibition of 
one or more hormones involved in the hypothalamus-pituitary-testis 
axis (Figure 1) will suppress spermatogenesis. GnRH secretion can 
be inhibited either by exogenous androgens via negative feedback, 
or by GnRH agonists. At the pituitary level, the stimulatory effect of 
GnRH can be blocked either by competitive binding of GnRH antag-
onists with GnRH receptors or by a GnRH antibody that binds GnRH 
before it interacts with its receptor. Progestins and exogenous andro-
gen inhibits secretion of LH and FSH, while inhibin can specifically 
decrease the amount of secreted FSH. Additionally, the effects of 
FSH on Sertoli cells can be blocked using either FSH immunization 
or GnRH antagonists; however, the only clinically-proven effective 
methods for men are androgen alone and androgen combined with 
other progestins or GnRH antagonists [for review, see (3)]. The use 
of FSH immunization, FSH antagonists, and inhibin for hormonal 
male contraception is in its infancy. For successful male-specific 
contraception, the production of LH, FSH, and consequently, intra-
testicular testosterone need to be massively suppressed, while the 
physiologic needs of peripheral androgens are required to be supple-
mented by exogenous means.

In the 1990s, two large international studies sponsored by the 
World Health Organization (WHO) (71, 72) tested testosterone 
esterinate (TE), by im injection, as a male contraceptive at a dose 
of 200 mg/week. Subjects did not use any other contraceptive for 
one year once their sperm concentrations had fallen below the set 
threshold. The overall pregnancy rate was 1.4% when jointly consid-
ering the azoospermia and oligozoospermia and an overall failure rate in prevent-
ning pregnancy of 3.2 per 100 person-years (73). The main disad-
vantages of using a testosterone-alone regimen are the inconvenient 
dosing method, pain of injection, slow onset (i.e., four months) 
and severe androgen-related side effects, including increased body 
weight, acne, and changes in serum lipoproteins and possible effects 
in the prostate. Additionally, azoospermia was only observed in 50 
to 70% of Caucasian men, whereas a higher rate (94%) of azoosper-
mia was achieved in an East Asian population using testosterone 
alone. Possible explanations of this heterogeneity in the spermatoge-
nic response include the sensitivity of hypothalamus-pituitary-testis 
axis to the negative feedback signal from testosterone (74), intra-
testicular 5α-reductase activity (75), pretreatment hormonal status 
(76, 77), and polymorphisms in the common polyglutamine stretch 
(CAG repeat) length in exon 1 of the AR gene (78).

To increase the response rate of hormonal male contraception in 
Caucasians and to avoid those disadvantages caused by supra-
physiologic doses of testosterone, other gonadotropin-suppression 
substances (e.g., progestins and GnRH antagonists) were included 
and used as combination regimens. The widespread use of GnRH 
antagonists for hormonal male contraception is limited because 
these proteins are expensive to synthesize and difficult to deliver. 
On the contrary, progestins have been used as a key component of 
female contraception for decades. The administration of progestins 
alone in men results in faster and more potent gonadotropin sup-
pression (79); however, nearly complete depletion of endogenous 
testosterone leads to loss of libido. Therefore, a physiological dose 
of testosterone was always included during most clinical trials. 
Additionally, testosterone and progestins work synergistically in sup-
pression of gonadotropins. The currently available progestins include 
cyprenestane acetate (CYP), depot medroxyprogesterone acetate 
(DMPA), norethisterone enanthate (NETE), levonorgestrel (LNG), 
desogestrel (DNG), etonogestrel (ENG), and didecylgesterol (DNG). 
Except for DMPA, all other progestins are orally active compounds, 
which are good candidates for inclusion in a male contraceptive 
“pill.” Clinical trials of hormonal male contraception are aimed at 
finding the best androgen-progestin combination and the mini-
mum effective dose of these compounds [for recent reviews, see (3, 
80)]. Many studies based on weekly or biweekly injection of TE in 
combination with oral or depot forms of progestins have shown pro-
found sperm suppression and tolerable side effects. Unfortunately, 
the major limitations of those studies to date have been the small 
population involved in each study and impractical dosing regi-
ments. Several novel regimens were studied recently, including a 
self-applied regimen using a testosterone transdermal patch plus 
DSG at doses of 75, 150, and 300 µg/day (81). Owing to the 
failure of delivering sufficient androgen, the azoospermia rate was 
significantly lower than those therapies consisting of TE or Triap-
letts combined with the same dose of DSG. More recently, a depot 

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testosterone/DMPA combination regimen was investigated in healthy men (82). Although this dosing regimen demonstrated high efficacy with little-to-no pregnancies observed, approximately one-half of the volunteers discontinued the study for various reasons. Additionally, the administration routes used in this study, implantation and im, were inconvenient despite the fact that the dosing frequency was relatively low. TU alone demonstrated promising efficacy, therefore, more recent studies have focused on long-acting androgens combined with potent progestins, such as TU + NETE and testosterone decanoate (TD) + ENG. In the most recent multicenter clinical trial involving 112 healthy men, treatment with 300 µg ENG daily plus 400 mg TD every four or every six weeks for forty-eight weeks achieved 93.5% and 82.5% azoospermia in the respective treatment groups (83). To date, progestins (e.g., norethisterone, desogestrel, and DMPA) combined with long-acting testosterone esters (e.g., TU and TD) appear to represent the most promising approach to hormonal male contraception.

No major toxicological effects were reported in most hormonal male contraception clinical trials involving young eugenital subjects. Besides the inconvenient administration routes, steroid-related side effects are the major limitations of testosterone-based male contraception and include decreases in HDL cholesterol, increases in hematologic parameters such as hemoglobin and hematocrit, increase in body weight, gynecomastia, and acne. Although lower doses of testosterone were effectively used in testosterone-progesterone combination regimens, similar but minor side effects were reported. Additional concern of long-term treatment with testosterone is the potential role of testosterone in the prostate and cardiovascular system, which needs to be evaluated by large and long-term prospective studies in the future.

To prevent potential adverse effect of androgen treatment on the prostate, tissue selective steroidal androgens, such as 17α-methyl-19-nortestosterone (MENT), were recently investigated for hormonal male contraception. MENT is an aromatizable but non-fat-reducing steroidal androgen, which demonstrated lower and twofold same potency as testosterone in the prostate and levator ani muscle, respectively, in castrated male rats and maintained sexual behavior in animals and in hypogonadal men. The antireproductive activity of MENT was recently studied in animals and men. High efficacy (with 100% infertile rate) was achieved using MENT alone or in combination with estradiol as hormonal contraception in adult male bonnet monkeys (84). Most recently, MENT’s reversible effects and its usefulness as a single-regimen hormone-driven male contraceptive have been investigated in early-phase clinical trials (85). MENT acute implants of differing doses were inserted subdermally at a larger delivery dose rate of 400 µg/day for twelve months. In the highest dose group, azoospermia was achieved in 72% of subjects, and 9% exhibited oligospermia. One was oligozoospermic and the remaining two were nonresponders. Previous pharmacologic studies in the monkey revealed that MENT maintained normal size of the prostate at the minimum dose required to suppress LH (86). Consistently, no significant difference in the size of prostate was observed before and after treatment in all drug treatment groups. Although the effective dose of MENT is much lower than that required in testosterone-based male contraception regimens, typical steroid-related side effects were similar to those reported in testosterone-based clinical trials. Additional pharmacokinetic studies showed that the total body clearance of MENT in both monkey and man, was much greater than that of testosterone. The long-term action of MENT after a single implantation in suppression of spermatogenesis makes it a promising candidate for hormonal contraception either alone or in the combination with progestins. Nevertheless, unfavorable pharmacokinetic properties, the requirement of parenteral administration, and steroid-related side effects are major limitations of MENT.

Major limitations associated with steroidal androgens can be largely overcome by novel SARMs. An arylationpropionamidic SARM, C-6, exhibited tissue selectivity in castrated male rats with higher andabolic activity (ED50, levator ani muscle = 0.68 mg/kg/day) than androgen activity (ED50, prostate = 3.1 mg/kg/day) (86). In the castrated male rat, levator ani muscle mass was maintained at a level similar to levator ani muscles from intact controls by C-6 at a dose of 1.2 mg/kg/day, whereas the mass of the prostate was only partially maintained (50% of control). At this dose, the elevated concentrations of LH and FSH in castrated animals were fully or partially suppressed, respectively. A pilot study of C-6 in intact male rats shows that this SARM significantly inhibits spermatogenesis at a single high dose of 4 mg/kg/day and maintains its tissue-selective pharmacologic activity in the muscle and prostate. Studies of spermatogenesis over a broad pharmacologic dose range of C-6 are needed to fully delineate its effects on spermatogenesis and its feasibility for male contraception. Additional pharmacokinetic studies of C-6 in rats have indicated that it is rapidly and highly (76%) absorbed after oral doses and is cleared slowly from the body (0.72 mL/min/kg). Although the effects of C-6 on hepatic enzymes—such as the aspartate aminotransferase AST-SGOT and the alanine transaminase ALT-SGP—and serum lipids were not evaluated in this study, previous pharmacology studies demonstrated the absence of significant changes in hepatic function and lipid profiles using other SARMs with same pharmacophore in the rat (33). Importantly, the minimum dose of C-6 required for LH suppression and full maintenance of levator ani muscle weight are similar, but at least two-fold less than that needed to fully maintain the prostate. Additionally, the favorable pharmacokinetic properties and oral bioavailability of SARMs make them amenable for an oral daily dose. Furthermore, SARM treatment appears to be free from unwanted side effects related to steroidal androgens. Taken together, these results indicate that some SARMs (e.g., C-6) are promising candidates for development as a component in a “male pill.”
TREATMENT AND PREVENTION OF BENIGN PROSTATE HYPERPLASIA (BPH)

BPH is a common disease associated with both aging and androgens. The principle intraprostatic androgen is DHT, which is converted from testosterone mainly by type 2 5α-reductase. Without treatment, long-standing BPH potentially leads to recurrent bladder infection, bladder calculi, acute urinary retention, and possibly the necessity of prostate surgery (87). Lower urinary tract symptoms (LUTS), commonly associated with symptomatic BPH, are caused by mechanical blockage of DHT-dependent hyperplasia and reduction of the urethral lumen diameter arising from contraction of smooth muscles under an increased α-adrenergic tone (88). Current drug treatments for BPH include androgen deprivation, phytotherapy, 5α-reductase inhibitors, and α1-Blockers. For patients with severe BPH, surgical treatments provide the most rapid and best relief of symptoms.

Androgen deprivation using GnRH analogs, such as leuprolide and goserelin, suppresses the production of gonadotropins and consequently testosterone synthesis, which significantly decreases the size of the prostate. However, severe side-effects related to androgen deficiency (e.g., loss of libido, hot flashes, and impotence) are inevitable (88). An extract from the American dwarf palm (Serenoa repens) is the most common phytotherapy for BPH. In fact, plant extracts are the first line of treatment for prostate enlargement and associated LUTS in Europe. Permelin, the n-homoe lupenisterolic extract of S. repens, is currently marketed in France and marketed in Europe. Efficacy studies of S. repens extract for BPH treatment suggest that it provides mild to moderate improvement in urinary symptoms and urinary flow comparable to that achieved by finasteride, but with less unwanted side-effects (89). Possible mechanisms of S. repens extract efficacy in BPH were recently reviewed and proposed, including antiandrogenic action, anti-inflammatory effects, induction of apoptosis, and antiproliferative activity (88). Understanding the mechanism of S. repens extract in BPH will likely provide a rational basis for the design of novel compounds with specific targets.

Based on the pathologic mechanisms of BPH, the clinically preferred medical treatment for BPH is either a 5α-reductase inhibitor or an α1-adrenergic blocker. Finasteride was the first available type 2 5α-reductase inhibitor. It reduces prostate size by blocking the conversion of testosterone to DHT in the prostate, thus inducing epithelial atrophy. Long-term finasteride therapy for BPH is effective and safe as proved by multiple efficacy and safety studies. Clinical trials have shown that finasteride consistently decreases prostate volume approximately by 19 to 27%, significantly improves symptoms, and decreases the risk of urinary retention and the likelihood of BPH-related surgeries in men with symptomatic BPH at a daily dose of 0.5 mg/day significantly decreased: 1) prostate size by 25%, 2) symptoms of obstruction, and 3) the risk of acute urinary retention or surgical intervention by 48% in a two-year clinical trial (94). A follow-up safety and efficacy study (95) showed no additional side-effects were observed after four-year treatment. There are no published studies directly comparing the efficacy of dutasteride and finasteride; however, comparison of end point markers from separate dutasteride and finasteride studies suggests that they exhibit similar efficacy and side-effect profiles. Additional common adverse effects associated with dutasteride were ear-nose-throat infections, musculoskeletal pain, and upper respiratory infections (96). The potential benefit offered by the more potent suppression of DHT with dutasteride is under investigation.

The α1-adrenergic receptor antagonists (i.e., α1-blockers) improve urinary symptoms by acting on the dynamic component associated with an α1-adrenergic receptor–dependent increase in smooth muscle tone: α1-Adrenergic receptors also play an essential role in regulating blood pressure, thus, developing α1-blockers with tissue-selective action for BPH is the main obstacle. Significant progress has been made in the past decade as evidenced by the discovery and development of several generations of compounds with increased efficacy and safety, namely from nonselective α1-blockers (e.g., phenolphthalamine) to selective α1A-blockers (e.g., prazosin, doxazosin, and terazosin) and then to tissue-selective α1-blockers (e.g., tamsulosin and alfuzosin) (for review, see review (94)). Combination therapy with a 5α-reductase inhibitor and a selective α1-blocker showed better efficacy than monotherapy with either component (96), indicating that such combination therapy is a promising regimen for the treatment of BPH.
SARMs acting as a partial agonist in the prostate but a full agonist in the muscle may provide a novel therapeutic approach for the treatment of BPH. The pharmacologic activity of the SARM S-1, hydroxyflutamide (antiandrogen), and finasteride (5α-reductase inhibitor) in intact male rats was recently reported (97). Additionally, S-1 (5, 10, and 25 mg/kg) selectively decreased the prostate weight and was equal in efficacy to finasteride (3 mg/kg). At the end of the nine-day treatment, no significant changes in levator ani muscle weight, plasma levels of testosterone, or FSH were observed in the SARM-treated group. Nonetheless, finasteride significantly increased testosterone concentrations in intact male rats. The SARM also showed very weak inhibition of human 5α-reductase enzymes, both types 1 and 2, suggesting a different mechanism in suppressing prostate size other than that of finasteride. These studies indicate that SARMs may be feasible for the treatment of BPH either as a single or combination therapy in the future.

**Future Directions**

Results from in vitro and in vivo animal studies suggest that the therapeutic promise of SARMs as treatment for muscle wasting, osteoporosis, hormonal male contraception, and BPH may be realized in the not so distant future. Demonstration of advantages, including tissue selectivity, favorable pharmacokinetic properties, AR specificity, and lack of steroid-related side effects, clearly distinguish these drugs from their steroidal predecessors and open the door for expanded clinical use of androgens. The best potential clinical application of SARMs is most likely to be the treatment of muscle wasting. The rapid and profound improvement upon treatment with testosterone makes muscle wasting an ideal and relevant target for early clinical trials and proof-of-concept studies with SARMs. As the molecular mechanisms of action of SARMs on target tissues become more fully understood, the discovery of novel SARMs and expansion into broader therapeutic applications will be more feasible. Currently, research on SARMs is in its early stages, namely preclinical discovery and the early phase of clinical development. Phase II studies planned in the next two to three years, however, should reveal the true promise of this exciting new therapeutic class of drugs. It will take years of efforts to deliver SARMs from the laboratory bench to patients. It is to be hoped that ideal SARMs with all of the beneficial pharmacologic activity of androgens without the unwanted side effects will provide individual patients with various androgen-dependent conditions a significantly improved quality of life.

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**References**

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The first report to demonstrate the potential of an orally bioavailable SARM for hormonal male contraception.


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Jiyun Chen, PhD, (left) was a graduate student and Presidential Fellow in Dr. Dalton’s laboratory at The Ohio State University. Her dissertation research focused on the structure-activity relationships for nonsteroidal selective androgen receptor modulators and their potential application to hormonal male contraception. She is currently a research scientist at Amgen, Inc., Thousand Oaks, CA. E-mail: chenjiyun@yahoo.com.

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