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Clark et al present results from phase I studies conducted with GSK2881078, a member of a new class of drugs known as selective androgen receptor modulators (SARMs). SARMs with varying chemical scaffolds and diverse pharmacologic properties have emerged since initial reports of their discovery in 1998 (1, 2). Analogous to selective estrogen receptor modulators (SERMs) which elicit differential pharmacologic effects on breast, bone and uterine tissues, SARMs provide the opportunity to selectively regulate muscle, breast, bone and prostatic tissues for therapeutic benefit. Differences in androgen receptor conformation, androgen receptor and steroid metabolizing enzyme expression between tissues, coactivator and corepressor recruitment, non-genomic signaling, and/or pharmacokinetics associated with variations in the chemical structure are thought to be strongly associated with the ability of SARMs to differentially promote muscle and bone growth and strength, inhibit the growth of breast cancer and shrink the prostate in animals and humans (3-9). Negro-Vilar (10) defined an ideal SARM for the treatment of male hypogonadism as one that is orally active, suitable for once daily administration, and capable of enhancing fat-free mass, muscle mass and strength, bone growth and libido, with lesser but stimulatory effects on the prostate, seminal vesicles and other sex accessory tissues.

Like other SARMs ahead of it in development, GSK2881078 appears to meet most of these criteria. It bound the human androgen receptor with high affinity and selectivity and restored the weight of the levator ani muscle of orchiectomized rats to that of sham-operated controls at a low dose of only 0.3 mg/kg/day, while only producing modest increases in prostate weight. In the healthy volunteers included within the phase I clinical trial presented herein, GSK2881078 demonstrated a terminal half of about one week and dose-dependent decreases in high density lipoprotein (HDL) and sex hormone binding globulin (SHBG). GSK2881078 was well tolerated. Although two subjects showed marked elevations in creatine phosphokinase (an adverse event not reported with other SARMs), elevations in alanine aminotransferase were infrequent. The pharmacologic effects of GSK2881078 on HDL and SHBG (established biomarkers for androgen activity in humans) were also similar to those observed for other SARMs (i.e., enobosarm and LGD-4033) (11,12), strongly suggesting that it too will have beneficial effects on body composition with longer-term treatment.

Although accumulating evidence strongly suggests that many SARMs have acceptable safety profiles and the requisite effects on body composition, proving that SARM-induced increases in lean body mass (i.e., muscle) are associated with improvements in physical function appears to the greatest barrier to their regulatory approval and clinical use. A variety of therapeutic agents with the ability to build muscle have been approved. Testosterone for example is approved for clinical use as testosterone replacement therapy, but not as a therapeutic agent to improve body weight, lean body mass or physical function. As such, clinical trials for new testosterone products use the restoration of serum testosterone levels as their primary efficacy endpoint. Such a clinical endpoint (i.e., demonstrating that reasonable serum

concentrations are achieved) is not feasible for a SARM. For the treatment of male hypogonadism, approval would almost certainly hinge on showing that the SARM ameliorates hypogonadal symptoms (e.g., deficits in muscle strength, bone mineral density or sexual function) in a large but otherwise healthy cohort of older men. Defining what constitutes a clinical deficit in these hypogonadal symptoms, and in turn defining what qualifies as a clinical benefit in ameliorating them, are challenging but necessary steps if a SARM is to ever be developed for hypogonadism.

More rigorous clinical endpoints have been required for other anabolic agents. Oxandrolone was first approved by the United States Food and Drug Administration in 1964 as adjunctive therapy to promote weight gain in patients who experienced weight loss following extensive surgery, chronic infections, severe trauma, corticosteroid use, or other undefined pathophysiologic reasons. Pivotal clinical trials for oxandrolone focused on its ability to increase body weight. Somatropin (i.e., human growth hormone) received accelerated approval in 1996 for the treatment of HIV patients with cachexia based on its ability to increase body weight and lean body mass and full FDA approval in 2003 based on a primary clinical endpoint of cycle work output (a measure of physical performance).

In a similar vein, recent phase III clinical trials examining the safety and efficacy of enobosarm for the prevention and treatment of muscle wasting in patients with stage III or IV non-small cell lung cancer (NSCLC) employed co-primary endpoints of lean body mass and physical function; the latter of which was assessed by as stair climb power (13). Phase III trials for anamorelin, an investigational ghrelin receptor agonist being developed for cachexia in NSCLC, utilized co-primary endpoints of lean body mass and handgrip strength (14). Statistically significant, clinically meaningful and similar benefits in lean body mass were observed with both drugs, but they were not accompanied by statistically significant improvements in physical function. The lack of strong association between lean body mass and physical function was presumably due to many confounding factors, including age, stage of disease, baseline physical function, chemotherapy regimen and toxicity, and a host of comorbidities (e.g., arthritis, edema, anemia, loss of appetite), that occur in patient populations like these, chosen amongst other reasons because they represent an un-met medical need in the eyes of regulatory authorities. Other diseases associated with muscle wasting or weakness like severe burns, chronic kidney disease, or knee replacement are likely to present different but similar challenges in clinical development. Ongoing clinical trials of SARMs in stress urinary incontinence and androgen receptor positive breast cancer will shed light on other possible routes for clinical development.

In summary, challenges in navigating the clinical and regulatory environment for approval in the US and Europe have perhaps had the greatest influence on the clinical development of SARMs. Numerous new chemical entities with nearly ideal pharmacologic and pharmacokinetic properties that are well tolerated and selectively increase lean body mass in humans have been developed. Yet, definitive

demonstration of the linkage between lean body mass and physical function in a relevant large patient population has remained elusive for a SARM. The clinical endpoints serving as their basis of approval have shifted with time and clinical indication and are likely to continue to do so as the field matures with additional safety and efficacy data pertaining to the relationship between lean body mass and physical function, regulatory decisions with SARMs and other agents, and yet unexplored clinical indications (e.g., Duchenne Muscular Dystrophy). Although it's been two decades since the initial discovery of a SARM, much work remains to be done before they can be used for muscle wasting or another condition. GSK2881078 has taken the earliest steps down this winding road.

Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [appropriate reference number], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [appropriate reference number(s)].

Conflict of Interest Statement

Dr. Dalton is an inventor on enobosarm patents through the University of Tennessee and The Ohio State University. He receives royalties on these patents and is a paid consultant to GTx, Inc. (Memphis, TN) who has licensed them.

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