Bankhead-Coley Cancer Research Program

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Department of Orthodontics *2007 Program*
University of Florida *Bridge (1-year project)*

Project Title: Androgen-Mediated Reversal of Muscle Wasting

Project Summary: Prostate cancer is the most common cancer affecting men in the United States based on 2006 American Cancer Society estimates and accounts for one-third of all new cancer cases. In Florida, the estimated number of new prostate cancer cases in 2006 leads all other cancers in both men and women and is 135 percent higher than breast cancer, the next most common carcinoma. Prostate cancer 5-year survival rate has increased to almost 100 percent over the past 20 years and is due to earlier detection and more effective therapies. Of all the common cancers, prostate cancer has the highest potential for a 100 percent survival at 15 years (currently 77 percent), but this achievement is dependent on the development of effective therapies that allow maintenance of the quality of life for the patient. Current management approaches include the use of hormone therapy to cease testosterone production or block testosterone receptor sites to effectively block the actions of testosterone and slow or halt the growth of prostate cancer. However, these approaches are not specific to the prostate and affect all tissues that depend on testosterone for maintenance, including muscle and bone. A recent approach in treating prostate cancer has been the use of a specific class of inhibitors that prevent the conversion of testosterone to dihydrotestosterone (DHT), a more potent form of testosterone. These medications, however, have additional side-effects that eventually may promote prostate cancer to a more deadly form. A new category of hormone therapy that appears promising for treatment of prostate cancer is the use of new novel non-steroidal selective androgen receptor modulators (SARMs). The newest of these compounds act on tissues selectively. For example, they minimally act on prostate tissue, while providing full maintenance of muscle and bone. In addition, these compounds cannot be converted to DHT. While initial studies of these compounds have been positive, there have been no studies that have evaluated testosterone-specific cellular and molecular responses to determine if the action of SARMs on muscle, bone, and prostate is comparable to testosterone. Muscle responds quickly to testosterone and thus muscle response provides an excellent indicator for testing the effects of synthetic testosterone-like compounds such as SARMs. Most skeletal muscles respond to testosterone by adding more muscle fibers and enlarging the existing ones. However, a small group of muscles react to testosterone in a manner similar to the reaction of the prostate. One goal of this grant is the evaluation of the response of different muscles to SARMs that may be specific for muscle and bone maintenance but minimally support prostate growth. The second goal of our research is to investigate one potential cellular mechanism that is responsible for many of the effects of testosterone and testosterone-like compounds on muscle. The mechanisms involved in testosterone-mediated maintenance of muscle are currently unclear. Understanding these mechanisms is an important advancement towards our ability to develop compounds that would specifically target muscle, but exclude activation of the prostate.