

Advancements in prostate cancer research provide hope for finding a cure and lead to the discovery of new treatments to minimize the impact of a man's prostate cancer and maximize his quality of life. This regular *Hot SHEET* supplement includes some of the latest research from the Prostate Cancer Foundation (www.pcf.org).

The PCF is the world's leading philanthropic organization funding and accelerating prostate cancer research. Founded in 1993, the PCF has raised more than \$745 million and provided funding to more than 2,000 research programs at nearly 200 cancer centers and universities.

Studying the Effects of ADT on Brain Function

Androgen deprivation therapy (ADT) is a primary treatment for prostate cancer, and acts by blocking the production or action of testosterone and other male hormones that activate the androgen receptor (AR). **Studies have suggested that ADT may affect cognition and has been associated with the development of Alzheimer's disease and dementia.** (See page 5 of this month's *Hot SHEET* for an example of such a study.) However, biological evidence to support this effect has not yet been demonstrated. Moreover, whether and how clinicians should act upon this knowledge when selecting treatments for patients is unclear. **Patients with prostate cancer are surviving for a longer time on ADT and more potent AR-targeted therapy (i.e. abiraterone, enzalutamide, and apalutamide). Thus, it is critical to understand if and how these treatments contribute to cognitive decline.**

Overall, cognition in men with prostate cancer can be affected by three categories of factors:

1. Genetic effects: Activity of the AR can be affected by differences in the gene that gives instructions for cells to make the AR protein; a larger, less active AR protein is associated with a higher risk of cognitive impairment when patients are treated with ADT
2. Patient effects, such as age and other co-occurring illnesses; androgen levels in the brain decrease with age
3. Drug effects: For patients on ADT, the ability of the drug to penetrate the blood-brain barrier and how effectively the drug targets the AR in the brain

How Does Testosterone Work in the Brain?

Androgen receptors (AR) are found in the brain and perform several critical functions. AR and testosterone play a role in memory, emotional function, and cognitive function in general. Low testosterone levels are known to impair these functions. Testosterone has also been found to protect brain cells from death. Thus, the brain may be an unintended target of ADT and AR-targeted therapy.

Two PCF-funded researchers aim to determine the contribution of each of these factors to cognitive impairment in prostate cancer patients being treated with ADT or other AR-targeted therapies. Dr. Alicia Morgans is an Associate Professor of Medicine at the Northwestern University Feinberg School of Medicine, and Dr. Charles Ryan is a Professor of Medicine and B.J. Kennedy Chair in Clinical Medical Oncology at the University of Minnesota. **Precision survivorship** is a field of medical research and clinical practice that aims to identify vulnerable populations at increased risk for adverse outcomes from cancer treatments, understand the biology and genetic factors underlying these effects, and use this information to select personalized treatments that will maximize a patient's long-term quality of life. **Dr. Morgans and Ryan's precision survivorship studies aim to identify patients who are at risk of cognitive impairment with AR-targeted therapies, and identify treatment strategies to prevent or reverse cognitive decline without compromising survival.**

One such study, called ARACOG, is a randomized phase 2 trial to **compare cognitive effects in men with advanced prostate cancer undergoing treatment with ADT + enzalutamide vs. darolutamide.** Enzalutamide has been found to cross the blood-brain barrier and penetrate the brain, while darolutamide (a new drug that is up for FDA approval) appears unable cross the blood-brain barrier. **These differences have led Drs. Morgans and Ryan to hypothesize that enzalutamide may cause cognitive impairment while darolutamide will not.** In ARACOG, men with castration-resistant prostate cancer who have not received prior second-generation AR-targeted therapy will be randomized to receive enzalutamide or darolutamide (+ ADT). Patients' cognitive function and brain activation (using functional MRI) will be evaluated at baseline and over the course of treatment, up to one year.

This study will contribute to the body of knowledge about treatments for advanced prostate cancer by defining the proportion of prostate cancer patients who have baseline cognitive impairment, characterizing the biology of the effects of low testosterone and AR inhibition in the brain, and comparing the cognitive effects of two different therapies. **Importantly, results will help to identify high-risk patients who can be selectively enrolled in future intervention studies.**

Talk to your doctor about whether enrolling in a clinical trial may be right for you.

For more information visit www.pcf.org, email info@pcf.org, or call 1-800-757-2873.