What’s So Special About the Androgen Receptor? …And The Potential Impact Of Galeterone

In a recent interview, we spoke with Dr. Fred Saad, a noted clinician and researcher from The University of Montreal Hospital Centers, about the Androgen Receptor (AR) and its relevance for prostate cancer.

**VHS:** Dr. Saad, Tell us what the androgen receptor is and why making it a target is beneficial to patients.

**FS:** The androgen receptor (AR) is a protein found in prostate cells that is activated by the binding of an androgen, which is a type of hormone, including testosterone, that control male characteristics. In some men, androgens also cause prostate cancer to grow by binding to a protein in prostate cells. Hormonal medicines (androgen deprivation therapy or ADT), which block the production of androgens, are routinely used to treat prostate cancer (PC).

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Can We Afford to Be Cured!

The Prescription Drug Affordability Act of 2015 provided some specific directives to improving patient access to care; namely the bill:

- requires the Centers for Medicare & Medicaid to negotiate lower prices on behalf of beneficiaries for drugs covered under Medicare Part D;
- accelerates closure of the Medicare Part D coverage gap known as the “donut hole,” under which beneficiaries who have reached a certain level of yearly drug costs become fully responsible for any additional drug costs up to a certain limit;
- requires drug manufacturers to issue rebates for prescription drugs dispensed to eligible low-income individuals under Medicare or Medicaid;

and

- expands the application of certain prescription drug rebate requirements under Medicaid to include rebates for generic drugs.
- amends the Federal Food, Drug, and Cosmetic Act to: (1) allow the importation by individuals of prescription drugs from Canada and, potentially, other countries; and (2) establish certain conditions on the award of market exclusivity with respect to drugs.

Yet, a recent Wall Street Journal report shows that the U.S. consumer pays more for drugs than any other country in the world. “In the case of Norway, U.S. prices were higher for 93% of 40 top branded drugs available in both countries in the third quarter. Similar patterns appeared when U.S. prices were compared with those in England and Canada’s Ontario province. Throughout the developed world, branded prescription drugs are generally cheaper than in the U.S.”

In this supposed patient-centric climate, why should this disparity exist and continue to be a point of contention between government and industry, much less patients themselves. Last week a group of U.S. Senate and House lawmakers, led by Reps. Lloyd Doggett and Peter Welch, along with Sen. Bernie Sanders, urged the Department of Health and Human Services and the National Institutes of Health to move to lower the cost of the prostate cancer drug, Xtandi (enzalutamide), which costs four times more in the United States than in other major countries.

The drug, which was developed at UCLA through taxpayer-supported research grants from the U.S. Army (CDMRP PCRP) and NIH, has an average wholesale price in the U.S. of $129,000. Yet the same drug, sold by Astellas Pharma, wholesales for $39,000 in Japan and Sweden and in Canada for $30,000. If U.S. residents are funding the bulk of research costs, why should they be paying unreasonably more to gain the same hope for survival as others globally?

The major endpoint projected for the approval of Xtandi to the U.S. Food and Drug Administration is that it showed proven survival outcomes for those taking it. But, if the patient can’t afford it, then its effectiveness is ZERO!
Too often now we see patients being confronted with the impossible situation of buying their medications vs. paying their mortgages or rent or buying food. It is abhorrent that pharmaceutical company profit-seeking should supersede the basic human right to a healthy life.

In 1963 Jessica Mitford wrote The American Way of Death, that detailed how the funeral industry preyed upon those in their deepest moments of grief and emotional suffering. Are we now seeing that same avarice played out in the struggle of those seeking to live. Perhaps, but until reason and rightness plays out, it is the compelling mandate for government to intervene to insure equitable access to medications and care for patients. Healthcare IS a human right, not a privilege.

PSA and the USPSTF: First Do No Harm?

The U.S. Preventive Services Task Force (USPSTF) recommendation against regular prostate specific antigen (PSA) screening for prostate cancer is controversial. While it may reduce the risk of over diagnosis and overtreatment, the reduction in intermediate and high risk cancer diagnoses raises concern because of the potential for delayed diagnoses of important cancers in men who may benefit from treatment, according to investigators reporting in The Journal of Urology®.

Prostate cancer remains the second leading cause of cancer death among men in the U.S., with nearly 30,000 deaths annually. Deaths from prostate cancer have declined by about 40% since the advent of PSA screening in the late 1980s, and 40-70% of that decline may be attributable to screening. However, radiation therapy and surgery have a negative impact on quality of life. The uncertain benefit of PSA based screening, combined with the complications associated with treatment, led the USPSTF to conclude in October 2011 that the harms of PSA based screening outweighed the benefits, leading it to recommend against regular screening.

“Our study was designed to assess the impact of the USPSTF recommendation on screening practices among urologists and primary care providers and the incidence of prostate cancer,” explained lead investigator Daniel A. Barocas, MD, MPH, of the Department of Urologic Surgery, Vanderbilt University Medical Center, Nashville, Tennessee. “We know there is decreased utilization of PSA testing in some institutions and health systems, but has the number of incident cases per month changed substantially since the draft guideline was issued?”

Investigators evaluated the effect of the USPSTF guideline on the number and distribution of new prostate cancer diagnoses in the U.S. They identified incident cancers diagnosed between January 2010 and December 2012 in the National Cancer Database and assessed the trend of new prostate cancers diagnosed each month before and after the draft guideline was issued, comparing their findings with colon cancer. This study helped quantify the potential benefits (reduced harms of over diagnosis and overtreatment of low risk disease and disease found in elderly men) and potential harms (missed opportunities to diagnose important cancers in men who may benefit from treatment).

The number of prostate cancer diagnoses dropped by more than 12% (1363 cases) in the month after the USPSTF draft guideline was issued and the number continued to drop, resulting in an overall decline of 28% in incident prostate cancer diagnoses in the year after the draft guideline was issued. By contrast, the number of monthly colon cancer diagnoses remained stable. Diagnoses of low, intermediate, and high risk
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Editor’s Note: A video with Dr. Saad explaining the Androgen Receptor can be seen at: http://www.oncologytube.com/index.php?page=videos&section=view&vid_id=1037981 or https://www.youtube.com/watch?v=cUteMtPtUyM

VHS: Can you explain the significance of the AR-V7 Splice Variant?

FS: The androgen receptor (AR) is a protein found in prostate cells that is activated by the binding of an androgen (such as testosterone). The binding of an androgen to this receptor is known as AR signaling. The growth and survival of prostate cancer tumors rely primarily on the functioning of the AR signaling pathway. In some patients, one end of the AR is missing—causing the AR to be turned on, producing androgens; the most common form is Androgen Receptor Splice Variant 7 (AR-V7), an abnormal version of the androgen receptor.

Several oral medications have recently emerged for the treatment of castration-resistant prostate cancer. These agents either suppress the synthesis of extragonadal androgens (abiraterone) or target the androgen receptor directly (enzalutamide). Several studies have suggested that patients who possess the AR-V7 slice variant expression have poor responsiveness to both enzalutamide and abiraterone.

Although enzalutamide and abiraterone represent breakthroughs in the treatment of metastatic castration-resistant prostate cancer (mCRPC), approximately 20 to 40% of patients have no response to these agents (primary resistance), and for patients who demonstrated an initial response to either agent, nearly all will develop secondary resistance.

VHS: You have been involved in the evaluation of a new drug, galeterone, in the treatment of advanced-stage prostate cancer. It is a novel,

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A growing body of data suggests that cholesterol and other lipids may be useful targets in the treatment of prostate cancers. Statins have already shown utility in protecting against aggressive prostate cancer, at least in part as a result of their cholesterol lowering effects.

“We have known for nearly 100 years that cancer perturbs metabolic pathways,” said Michael R. Freeman, PhD, Director of Cancer Biology and Therapeutics and Biomedical Sciences at Cedars-Sinai Medical Center. “Prostate cancer up-regulates lipogenic pathways, and more so in more aggressive disease.”

Dr. Freeman discussed current research efforts to understand the role of cholesterol and other lipids. High levels of circulating cholesterol activate oncogenic pathways and inhibit tumor cell apoptosis to promote prostate cancer progression, he noted. The impact is so potent that mice with high circulating levels of cholesterol show an increase in prostate cancer even after castration.

“Cholesterol is a central metabolite in lipid metabolism, inflammatory responses and other elements of cancer promotion and progression,” Dr. Freeman said. “It’s also a precursor to
androgens, estrogen and other hormones that are active in prostate cancer. High circulating levels of cholesterol can cause the accumulation of androgen in tumor cells even in the presence of normal levels of circulating androgen.”

Androgens and cholesterol have mutually beneficial effects in prostate cancer. Androgens promote lipid accumulation in prostate cancer cells and the androgen receptor up-regulates transcriptional activators of fatty acid and cholesterol synthesis. The net effect is to increase accumulation of lipids in prostate cancer cells.

At the same time, androgens downgrade cholesterol efflux mechanisms in prostate cancer cells. And while high low-density lipoprotein (LDL) cholesterol levels retard the growth of epithelial cells in the normal prostate, high LDL cholesterol levels also stimulate prostate cancer cell growth.

“The clinical implication is that drugs such as statins that reduce cholesterol may affect the progression of prostate cancer,” Dr. Freeman said. “We have seen that the use of statins after surgery is associated with a 30 percent lower risk of recurrence of prostate cancer. And the effect is dose dependent.”

As a major component of cell membranes, cholesterol imposes a structural order by partitioning the plasma lipid membrane into discrete micro domains. These micro domains increase oncogenic signal transduction, suggesting that any disruption to the accumulation and organization of cholesterol could disrupt these micro domains and inhibit signal transduction. Targeting cholesterol metabolism may also potentiate immunotherapy in prostate cancer. The data are unclear, in part because prostate cancer tumors are heterogeneous.

Dr. Freeman’s laboratory has developed a novel RNA-based profiling and classification system for prostate cancer tumors. The profiling system has been validated in a variety of preclinical systems, as well as in metastatic human prostate cancer. “Statins are clearly chemoprotective against aggressive prostate cancer,” Dr. Freeman said. “Prostate cancer subtyping may allow approaches to patient stratification that will improve our current rates of recurrence and slow disease progression.”

Further Defining “Personalized Medicine”

As scientists and clinicians further delve into the distinct genetic makeup of patients to determine causal factors of disease occurrence, this same information will be essential in choosing the appropriate treatment protocol.

At core of this research is the understanding of the genotype and phenotype of the disease present in the cancer cells of each patient. The genotype is the set of genes in our DNA which is responsible for a particular trait. Examples of genotype are:

- eye color
- hair color
- height
- certain diseases, which is important when we look at certain population groups and the incidence and/or mortality within that group; for example, the disproportionately high rate among African-Americans and prostate cancer.

Genotypes can only be determined by biological tests, not observations. Genotype is an inherited trait and hereditary information passed by the...
Impact Of Therapy On Gene Expression In High-Risk Prostate Cancer

One of the important posters presented at the recent ASCO-GU Symposium focused on the recurrence of prostate cancer after treatment with neoadjuvant docetaxel and androgen deprivation therapy.

Dr. Himisha Beltran, the lead author, discussed the problems in addressing the complex mechanisms of resistance and/or prognostic risk stratification for patients after primary treatment for prostate cancer. Her study evaluated 40 untreated and post-treatment tissue specimens as well as patient-matched pre-treated needle biopsies and baseline clinical data from patients enrolled on CALGB 90203: a randomized phase 3 trial comparing neoadjuvant docetaxel and ADT followed by RP vs RP alone for men with high risk localized PCA.

Results showed significant upregulation of Androgen Receptor and the ARv7 expression following treatment, as well as a subset of neuroendocrine genes. There was an overall higher AR score in treated cases (based on expression of 30 AR signaling genes) compared to untreated, along the spectrum of CRPC. This suggests that treatment using many of the new agents, e.g. abiraterone, enzalutamide, etc. might have a promoter effect on other forms of prostate cancers.

Further studies are in work in order to better understand the mechanisms of action. Information on the relevant clinical trial can be seen at:

https://clinicaltrials.gov/show/NCT00430183

Defining Quality In Your Healthcare

A friend and colleague, Dr. Arnon Krongrad, has over the past decade reformed the dialogue between patient and physician as to the delivery of services.

Dr. Krongrad recently posted this comment: “Healthcare demands choice and quality. Perhaps nowhere is this demand more acute than in surgery, where the results are often as irreversible as they are dramatic. But what is surgical quality? And is there consensus on its definition?”

As patients we are told we must make informed choices in our healthcare decision-making, but how can we do this intelligently and with certainty? Particularly with prostate cancer, where surgery has been held up as the “Gold Standard” therapy, how do we know if surgery is the best option for the stage of our disease; what type of procedure should we choose; what doctor is the best one for the procedure; and what should it cost?

A previous post from November 24, 2015 featured Dr. Karim Touijer from Memorial Sloan-Kettering Cancer Center providing some guidance for patients and their families on this as well as discussing the shift in treatment protocols using multidisciplinary elements in managing locally advanced prostate cancer.

One of these emerging elements of patient benefit from Dr. Krongrad is Surgeo, which is an online tool and service of the healthcare logistics company Allevion, Inc. that helps you simplify the process of searching for and choosing a surgery package that best serves your needs. It lets you compare these packages by surgeon, price, and location and delivers quality, value, and convenience through choices of surgery packages.

You may ask, “Aren’t we putting price into an equation about health?” Well, yes we are because, by government definition, we are all “consumers” of healthcare - not patients, not survivors, not people, but consumers. We are factors in the budgeting of government spending...
Your Brain On Drugs: Cognitive Impact of Therapy

A recent article in Cancer world discussed the issue of cognitive impact, or chemobrain, on patients being treated with endocrine therapies.

It has long been known that patients being treated with chemotherapeutic agents will often have changes in mental function with regard to learning and memory, speed of information processing, and executive functioning. But what is now being seen with many new drugs in the broad class of hormonal therapy, such as aromatase inhibitors, including abiraterone and enzalutamide, is the emergence of new side effects affecting cognition and development of neuroendocrine tumors.

A recent review that summarises more than a decade of research indicates that cognitive decline affects 20–60% of patients after chemotherapy (CA Cancer J.Clin 2015, 65:123–138). However, most studies have not been designed to address the effects of endocrine therapy, either alone or in combination with chemotherapy. Furthermore, since guidelines permit the choice between different endocrine regimens, knowing how each option could potentially impact on cognition might influence the decisions made in individual cases.

Multiple studies have indicated that aromatase inhibitors (AIs) and tamoxifen can cross the blood–brain barrier and enter the brain. All AIs inhibit both ERα and ERβ activity. The article goes on to state: “With multiple clinical trials indicating prolonged adjuvant endocrine therapy improves outcomes for breast cancer patients, the value of these treatments in managing breast cancer (ed. note: and by extension, prostate cancer) remains beyond doubt. Nevertheless, studies suggest endocrine therapy can potentially have adverse effects on cognitive function.

Attention needs to be paid to whether the observed changes in cognition associated with cancer therapies adversely impact aspects of everyday functioning that matter to patients, such as employment. Elucidating the clinical significance of side effects further would help to identify the therapies that have least impact on physical and mental morbidity.

In summary, we are in a brave new world of cancer therapeutics that can extend survival for many advanced stage disease patients; however, because of the intense personalization of the disease among individuals, we cannot characterize a one-size-fits-all approach to treatment. The necessity for research on biomarkers that can determine the most appropriate protocol for each patient is critical. Until then, the dialogue between physician and patient must be thorough and in-depth as to potential and expectations for success in treatment and in forward quality-of-life.

Further Defining...

In The Know

parents determines genotype. The entire genetic information about an organism is contained in a genotype – even those characteristics which are not expressed visually.

The phenotype is the physical expression, or characteristics, of that trait. Thus, as we look at patients groups in which certain clinical or disease expressions appear, the need is then try to characterize those common traits that will respond to specific therapies and establish a protocol for patients.

Much of this work is still being researched, but the need for better diagnostic markers based on genetic testing will drive that work. See this commentary from Dr. Christopher Logothetis of MD Anderson Cancer Center on the subject.

https://www.youtube.com/watch?v=npCQ0dzqT4Y

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first-in-class compound that disrupts androgen receptor signaling in several ways. Tell us about it.

FS: In the ARMOR3-SV study, patients with the AR-V7 expression are identified by a clinical trial assay, which detects the presence of the AR-V7 transcript in isolated circulating tumor cells (CTCs) in a blood sample (liquid biopsy). This marks the first CTC-based assay in a pivotal trial for prostate cancer and thus, is the first precision medicine development approach in prostate cancer.

ARMOR3-SV is designed to evaluate whether administration of galeterone will result in a statistically significant increase in radiographic progression free survival as compared to enzalutamide in mCRPC patients whose prostate tumor cells express the AR-V7 splice variant.

Editor's Note: View a discussion by Dr. Saad on the background for this study: http://www.oncologytube.com/index.php?page=videos&section=view&vid_id=1037992 or https://www.youtube.com/watch?v=QsuNcrETECg&spfreload=5

VHS: In the ARMOR3-SV study you will be comparing galeterone against another drug agent, enzalutamide (Xtandi). Why this particular comparison?

FS: Enzalutamide is anticipated to be a commonly used therapy (by both urologists and medical oncologists) in metastatic, treatment-naïve (Treatment naïve patients are those who have not received therapy with abiraterone acetate (ZYTIGA), enzalutamide or chemotherapy.) CRPC patients. In addition, galeterone, like enzalutamide, targets the androgen signaling pathway. Of note, at the present time, physicians continue to treat these patients with enzalutamide and abiraterone. Patients who express AR-V7 have been shown to have poor responsiveness to both enzalutamide and abiraterone.

VHS: Tell us about those patients who are candidates for this trial; what are the parameters to participate?

FS: To qualify for participation in ARMOR3-SV, patients must not have yet received any prior abiraterone or enzalutamide or chemotherapy for mCRPC, and they must express AR-V7 messenger RNA in circulating tumor cells as determined from an initial blood test. If the patient is determined to be AR-V7-positive, he may enter formal screening for participation in ARMOR3-SV.


Additionally, a video featuring Dr. Saad has been produced for physicians to consult with their patients on potential participation; it can be seen at: http://www.oncologytube.com/index.php?page=videos&section=view&vid_id=1037985 or https://www.youtube.com/watch?v=4P3MViCPv4A

VHS: What are the side effects associated with galeterone?

FS: Approximately 90% of side effects believed to be related to galeterone were considered mild to moderate in severity. The most common side effects reported in past clinical studies of galeterone are nausea (34%), fatigue (33%), itching (26%).

VHS: How many medical centers are participating in this trial, and where can we find more information?

FS: Over 100 clinical centers in 9 countries (Australia, Belgium, Canada, France, Germany, Italy, United States, United Kingdom and Spain)
are enrolling patients for ARMOR3-SV.

If a patient is interested in participating in ARMOR3-SV, or has additional questions, we recommend talking to your doctor or visiting www.clinicaltrials.gov for more details. More information, including a full list of clinical trial sites, is also available at www.tokaipharma.com.

Editor’s Note: To help in expanding the communication around this subject, we have produced a series of 11 podcasts that are available for listening or downloading on our new Prostate Net Radio Channel.

You can begin by going to: http://yourlisten.com/theprostatenet/dr-fred-saad-on-the-androgen-receptor

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Defining Quality…

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prostate cancers all decreased significantly, but new diagnoses of non-localized disease did not change. The decreases were similar across all subgroups of age, comorbidity, race, income, and insurance.

The study showed that 12 months after the draft guidelines were published diagnoses of new low risk cancers had fallen by 37.9%, and continued to fall more rapidly than other disease risk strata, suggesting that, in this regard, the USPSTF recommendation had its intended effect. Similarly, new diagnoses had fallen by 23.0-29.3% among men over age 70 and by 26.0% among infirm men, populations at risk for harms of treatment but unlikely to live long enough to benefit from early detection.

However, the study also identified a drop of 28.1% in diagnoses of intermediate risk disease and 23.1% in high risk prostate cancer one year after the draft guideline, which could result in missing important opportunities to spare men with higher risk cancers from progressive disease and cancer death.

“While some of the effects of this guideline may be beneficial in terms of reducing harms of over diagnosis and overtreatment, the reduction in intermediate and high risk cancer diagnoses raises concern for delayed diagnoses of important cancers associated with inferior cancer outcomes,” noted Dr. Barocas. “Future research should focus on prostate cancer screening paradigms that both minimize harms and maximize the potential benefits of screening, as well as accounting for individual patient risk factors and preferences.”

Editor’s Note: The issue of undiagnosed higher risk categories is forcing re-consideration of the USPSTF’s recommendation on screening. In reality, many doctors have ignored it and continued to utilize the PSA test because there is no other viable alternative for determining potential disease risk. Men should become knowledgeable as to their potential risk level and engage actively with their doctors to insure active personal health responsibility.
The Prostate Net® is a non-profit patient education and advocacy organization founded 18 years ago by Virgil Simons, a 20-year survivor of prostate cancer and a patient advocate. The Prostate Net has become an international organization that uses a matrix of informational techniques to address disease risk awareness and early disease interdiction.

The core objective of The Prostate Net’s mission is to:

1. Educate consumers most at-risk from a diagnosis of prostate cancer
2. Inform the community on other diseases and conditions of negative impact
3. Motivate consumers to make informed choices as to healthcare and lifestyle management
4. Provide on-going health care interaction between patient and professional communities
5. Create an interactive network to maximize actionable healthcare messages

The strength of The Prostate Net’s mission is aided by organizations with which we are associated: American Society of Clinical Oncology, Department of Defense Prostate Cancer Research Program, American Association for Cancer Research and European Association of Urology among others.

Our active initiatives include, but are not limited to:

Education:

- Patient and professional Website - www.theprostatenet.org
- Spanish language site - http://theprostatenet.org/espanol/

Research:

- Continuing partnerships with university based community studies
- Consulting relationships to local government agencies; materials for patient education/recruitment; training of agency staff, etc.

Community Interventions:

- Gentlemen, Check Your Engines™, focuses on Men’s & Women’s health issues featuring on-site health education and testing - http://theprostatenet.org/programs.html

Through the 17 years of our existence we have expanded our reach throughout the U.S. and to more than 50 countries. Our overarching objective is to continue to provide service to an expanding range of consumer, healthcare, government, university and service agencies to aid in reducing health disparity through education, research and community intervention. We inform to fight.

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