**What We Are About**

Our Group offers the complete spectrum of information on prevention and treatment. We provide a forum where you can get all your questions answered in one place by men that have lived through the experience. Prostate cancer is very personal. Our goal is to make you more aware of your options before you begin a treatment that has serious side effects that were not properly explained. Impotence, incontinence, and a high rate of recurrence are very common side effects and may be for life. Men who are newly diagnosed with PCA are often overwhelmed by the frightening magnitude of their condition. Networking with our members will help identify what options are best suited for your life style.

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Chuck Grim, Meeting Set-up

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**Next Meeting**

**April 20, 2019**

10:00AM to Noon

Meeting at Sanford-Burnham-Prebys Auditorium
10905 Road to the Cure, San Diego CA 92121
SEE MAP PAGE 10

**PROSTATE CANCER**

2 WORDS, NOT A SENTENCE

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**Functions Needed:**

1. **President:** IPCSG public relations, research and advice. Lyle LaRosh has performed for 18 years. 619-892-3888
2. **Vice President:** Support all team members, assist in monthly planning and speaker acquisition. Currently vacant Gene Van Vleet has performed Functions 2, 4, 5 for 11 years. 619-890-8447.
3. **Meeting facilitator:** Monthly planning and speaker acquisition. George Johnson has performed for 8 years. 858-456-2492
4. **Treasurer/Secretary:** Handle banking, accounting, government reporting (see 2)
5. **Hot Line:** Communicate directly with newcomers and handle phone inquiries. (see 2)

**IPCSG** is a 501c3 non-profit organization and all positions are performed gratis.

*(Continued on page 2)*
March 2019 Informed Prostate Cancer Support Group Meeting:
Dr. Rana McKay – Evolving Paradigms of High-Risk and Advanced Prostate Cancer: Novel Trials and Genomics
Summary by Bill Lewis

Although prostate cancer (PCa) leads the statistics for new cancer cases annually, at 19% of the total, deaths from PCa are far fewer than from lung/bronchial cancer: 9% vs. 26% of the total (and comparable to death rates from colon/rectal cancer and pancreatic cancer). Number of cases diagnosed spiked about 1990 after the PSA test was introduced, then plateaued for a decade. It has dropped due to the recommendation (since modified) against routine PSA screening. Deaths due to prostate cancer have been declining since their peak in the early 1990’s, due to the many treatments now available and advances made in surgery, radiation and ADT (androgen deprivation therapy), including new drugs such as Abiraterone (Zytiga), Enzalutamide (Xtandi), Apalutamide (Erleada), and Radium-223 (Xofigo), complementing or as alternatives to chemo drugs such as Docetaxel (Taxotere) or Cabazitaxel (Jevtana).

The promise of “Precision Medicine” is that DNA analysis in blood, urine and/or tissue may show what therapy will be most beneficial to the patient, avoiding ineffective treatments. Current DNA analysis methods are called “Next Generation Sequencing (NGS),” and may be paid for by Medicare (but only once – so when to test needs to be decided!) in cases of recurrent/relapsed, refractory, metastatic, or advanced (stages III or IV) cancer. Testing of the DNA from tumor cells (called “somatic” testing) is typically done on tissue or from a blood sample, and may involve sequencing the whole genome (the entire DNA sequence), the whole exome (the part that codes for proteins), or a “panel” of about 300-500 known cancer genes.

DNA testing may also be performed on “normal” cells, showing the genetic code you were born with. This is called “germline” testing, and is typically done on saliva or a blood sample. Results impact when / how often cancer screening tests would follow, and may lead to testing of relatives for their benefit. It can impact treatment, such as choosing PARP inhibitors or platinum chemotherapy.

Germline testing of about 700 men with metastatic prostate cancer (PCa) showed 12% had DNA-repair gene defects (mostly BRCA2, ATM, CHEK2 and BRCA1), whereas 5% of men with only localized PCa had such defects. Patients without cancer had only a 3% frequency of such defects. So, the NCCN (National Comprehensive Cancer Network) recommends consideration of genetic testing for metastatic prostate cancer patients and also for those with high or very high-risk localized disease.

Somatic testing: The genomic “landscape” of variations in metastatic CRPC (castrate resistant prostate cancer) tumors is being studied at multiple institutions. DNA repair pathway mutations were found in 34 (23%) of 150 patients tested so far. [Note the higher percentage of mutations found in these tumor cells vs. the 12% mentioned above for defects in corresponding normal/germline cells!] These mutations were in the “homologous recombination” pathway for DNA repair. An alternative pathway exists and is called “base excision repair.” The BRCA mutation is an example of the former. So-called PARP1 inhibitors can block the second path. In combination, DNA repair is blocked, and the cell dies. This is called “synthetic lethality.”

Various PARP inhibitors are being studied, including Olaparib, Veliparib, and Durvalumab. In patients with homologous recombination pathway mutations (i.e., defects), the drugs were about 90% effective in several different studies shown. The FDA granted Breakthrough Therapy Designation for Olaparib (Lynparza) in 2016 as monotherapy of BRCA1/2 or ATM gene mutated mCRPC patients after taxane-based chemotherapy and Zytiga or Xtandi. This is one example of the effectiveness of “precision medicine.” Other examples include immunotherapies and PSMA-targeting radiopharmaceuticals (e.g., Lutetium). Slide 26 has a more complete list.

What we know so far about the genetics of prostate cancer is that numerous genetic events/issues contribute to the development of PCa, and that advanced disease has more complex genetics. Which genetic events are relevant for indolent or aggressive disease are unknown. Patients can help drive the field forward by participating in clinical trials, and the IRONMAN registry.

(Continued on page 3)
The registry is for men with advanced prostate cancer, collecting information about a man’s type of prostate cancer, his treatments, and side effects experienced. It will also collect blood samples and health surveys relating to quality of life. It is targeting enrollment of 5,000 men in 9 countries. Contact: Call 858-822-6185 and speak to Lauren Stewart (Admin. Assistant) or Jennifer Palomino (Clinical Research Coordinator). See also https://vimeo.com/245833493 for a short video promoting the registry.

In the US, there is also the Metastatic Prostate Cancer Project. Note that only 5% of U.S. cancer patients are enrolled in clinical trials, which are almost always at research centers based in large cities. However, 85% of U.S. cancer patients are treated in community settings. The database will engage more cancer patients, and directly partner with them. Both saliva and “liquid biopsy” kits are provided. Over 650 men have enrolled since launch in January 2018. The project doesn’t give personal genetic results back to the patient, but it helps future generations, including better clinical trials and drug development targeting. See MPCproject.org.

In conclusion, novel treatment strategies are evolving for men with high risk and advanced disease. Genetic profiling of tumor tissue and of normal tissue has the potential to improve prognosis and treatment. Clinical trial and database participation will advance the field, to improve survival and quality of life.

Contact information: New patient appointments – call Lauren Stewart (see above).
Clinical trial portfolio – https://health.ucsd.edu/clinicaltrials
More information about prostate cancer –
https://health.ucsd.edu/specialties/cancer/programs/urologic/prostate or www.PCF.org

Questions:
What is the cost of the genetic testing? $2-3,000 without insurance, but most insurance covers it, or there are grants available to help out.
Can there be bladder issues when on chemo? There is no direct toxic effect, but the immune suppression can lead to infections, etc.
Genetic testing was done on the prostate. Should bone metastases also be tested? Ideally, yes, but the bone is hard to test, because typical handling of bone biopsies involves acid treatment – which destroys the DNA. It has to be done in a research center, such as the Moores Cancer Center.
What is the cause of gene mutations in the tumors? Different selective pressures lead to more prevalence of cells that have evolved into one DNA variant or another.
What about diet? It’s huge. A balanced diet is important. See downloadable guide at Prostate Cancer Foundation. Omega-3’s, Vitamin D, Calcium, etc. Fish and chicken are good sources of protein. She recommends “raw” forms of supplements rather than pills. One supplement, muscadine (a grape seed extract) is being tested by UCSD and Johns Hopkins against biochemically recurrent PCa.

After prostate removal, does PSA mean there is a metastasis? Only prostate cells produce PSA, but there can be PSA without a visible tumor. If there is microscopic disease, it may not be visible on scans, and the patient would be considered to be (as yet) non-metastatic. When there is such PSA recurrence, the patient should see a medical oncologist.

Differences and advantages of blood vs. tissue sampling for genomic testing? Circulating free DNA in the bloodstream may be from cancer cells, or could be from normal cells, not even prostate cells. It hasn’t been shown that blood tests correlate fully with tissue tests. Get tissue whenever possible.
Role of prostate and pelvic irradiation for a patient with metastases and hormone-resistant rising PSA? There are no clinical trial reports that give distinct guidance. If a large tumor in the prostate, possibly yes, less so if not. Also depends on how aggressive the patient wants to be, in the face of side effects.
A patient with a lymph node tumor, on Zytiga (and ADT, of course), is contemplating irradiation but wonders about getting a genetic test before the radiation. Depends on how accessible the lymph node is, and other factors.
What exactly does a medical oncologist do? Often coordinates care, especially for advanced PCa.
What about neuroendocrine cancer appearing in patients who have been heavily treated for advanced PCa? It does occur in about 10-15% of patients, but it’s not a reason to not get treated! There are studies underway on
the use of immunotherapies for neuroendocrine disease.

If the PSA is declining on hormone therapy, is there still a chance of tumors growing, that don’t express PSA? Yes and no. Depends on the clinical context and the patient’s history.

Does sugar feed cancer cells? Yes and no. All cells need sugar. If not available in your diet, the body will break down your muscles and make sugar. So don’t get extreme in avoiding sugar, but do limit refined sugar.

Androgen annihilation clinical trials? Lupron vs. stronger anti-androgens is being evaluated, for time to metastases.

Xgeva vs. Zometa pros & cons, and bone health? They are intended to prevent “skeletal related events,” including fractures. Xgeva is given as an injection every 4 weeks (with longer intervals being studied), and can cause low calcium levels and/or osteonecrosis of the jaw. Zometa is given by IV over 15 minutes every 12 weeks. It can cause a short-term reaction, treated with ibuprofen, and low calcium, and (rarely) osteonecrosis of the jaw. It can exacerbate kidney problems. Xgeva is considered a little more effective than Zometa. Both drugs were approved before Zytiga, Xtandi, etc. became available, and those drugs may provide better enough treatment of PCa so that these drugs may be needed less for advanced cancer patients. For patients still on classic ADT, which causes bone loss, these drugs are used to help strengthen the bone (if a DEXA bone density scan shows loss).

Are the genomics of tumor cells in the prostate always different from metastases? Most of the time, there are differences. Usually, she starts with prostate testing, and she likes to do it early – since it takes 4-6 weeks to get results. Then any soft tissue metastases can be considered. Different mets may have different genomics. A fast-growing bone met might be sampled if possible. It depends on the individual case details.

Is she running a clinical trial for mCRPC using a PARP inhibitor? Yes, combining Xofigo (radium-223) with Olaparib for patients with low volume lymph nodes and bone metastases. Enrollment is open.

Relative importance of genomics for diagnostics, vs. imaging tests? Imaging is to detect tumors. Genomics is for deciding how to treat the disease.

More info about muscadine? It’s being tested for biochemical recurrence, without metastases. It comes from grape seed extract. We don’t yet know if it is effective.

What about Provenge for non-metastatic PCa? A clinical trial is in progress.

After radiation to a metastasis, is ADT advisable? Thinking is changing. Trials are in progress. There isn’t a right answer. It depends on the patient’s attitude toward side effects, and desire to treat actively.

More details are given in the video of this presentation, including the PowerPoint slides, which will be available for purchase via the website shortly before the next meeting, or at the April meeting on the 20th.

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**Next IPCSG Meeting Speaker**

Presenter is Matt Kocher of Arc Men’s Health Clinic. This clinic, located in Mission Valley San Diego and San Francisco, offers the SwissWave Protocol acoustic wave therapy for erectile dysfunction and Peyronie’s Disease. They are dedicated to providing men with the highest quality, non-invasive treatment for erectile dysfunction. The SwissWave Protocol is a series of short, painless treatments to the penis using pulsating acoustical sound waves. It opens the blood vessels in the penis which is essential for an erection. This approach is also known as Acoustical Wave Therapy or AWT.

- **For further Reading:** [https://spendergast.blogspot.com/2019/03/prostate-cancer-news-of-interest-for.html](https://spendergast.blogspot.com/2019/03/prostate-cancer-news-of-interest-for.html)
- **For Comments, Ideas and Questions,** email to Newsletter@ipcsg.org
We need to find more active targets for new drugs. This will allow us to interact with different targets. Right now, we have several trials with PARP inhibitors and checkpoint inhibitors targeting the AR, except for radium 223 dichloride (Xofigo). In the future, the main challenge will be to develop new agents that will be able to interact with different targets. Right now, we have several trials with PARP inhibitors and checkpoint inhibitors. We need to find more active targets for new drugs.

Enzalutamide/docetaxel combo improves PFS, but not OS in frontline mCRPC

The combination of enzalutamide (Xtandi) and docetaxel improved 6-month progression-free survival (PFS) rates compared with docetaxel alone in patients with previously untreated metastatic castration-resistant prostate cancer (mCRPC), according to data from the phase II CHEIRON study.

In the study, patients were randomized to receive either docetaxel at 75 mg/m² for 8 cycles every 3 weeks, plus prednisone at 5 mg, or the same treatment plus enzalutamide given at the standard dose of 160 mg daily for 24 weeks.

Results showed a 6-month PFS rate of 89.1% in patients treated with the addition of the androgen receptor (AR) inhibitor compared with 72.8% in patients treated with single-agent docetaxel (P = .002). At a median follow-up of 20 months, the median PFS was 10.1 months versus 9.1 months in favor of the combination arm (HR, 0.71; 95% CI, 0.54-0.94; P = .01). However, the combination was not found to improve median overall survival (OS) compared with docetaxel alone at 29.6 months versus 33.7 months, respectively (HR, 1.13; 95% CI, 0.75-1.71; P = .5).

Major grade 3/4 hematologic toxicities observed with the combination consisted of anemia and neutropenia. Febrile neutropenia was observed in 10 patients who received the combination compared with 5 patients who received docetaxel by itself. Furthermore, grade 3/4 neutropenia was seen in 23 patients treated with the combination and 19 patients treated with docetaxel alone.

Lead study author Orazio Caffo, MD, director of medical oncology at the Santa Chiara Hospital in Trento, Italy, said that other novel agents are being explored with docetaxel, including the PD-1 inhibitor pembrolizumab (Keytruda) in the ongoing KEYNOTE-365 study (NCT02861573).

In an interview with OncLive, Caffo discussed the CHEIRON trial findings and their implications on the treatment paradigm in mCRPC.

OncLive: What was the rationale for combining these 2 agents in the CHEIRON study?
Caffo: Today, docetaxel and enzalutamide are the consolidated frontline treatments for patients with mCRPC. According to the different mechanisms of action, there is a strong rationale for combining these 2 treatments. Docetaxel acts mainly on the microtubule machinery, thus being able to interfere with the AR and also with cellular duplication. On the other hand, enzalutamide acts mainly on AR machinery.

What were the key findings from the study?
We enrolled patients with previously untreated mCRPC and they were randomized to receive either docetaxel alone given for 8 cycles every 3 weeks, plus prednisone at 5 mg, or the same treatment with the addition of enzalutamide given at the standard dose of 160 mg daily for 24 weeks. Patients were stratified based on pain and visceral involvement. As a primary endpoint, it is the rate of patients without progression at the end of the treatment. We have several secondary endpoints, such as objective response rates, PFS, OS, safety, pain, and quality of life. We saw a PFS rate of about 89% in terms of the primary endpoint in 246 patients.

What are the next steps with these data?
Today, in the actual landscape of mCRPC, it is very difficult [to move new therapies through the pipeline]. Many of the pharmaceutical companies are focusing on early-stage disease. The data from this study may be considered a proof-of-concept for future development of combinations comprised of newer agents, such as apalutamide (Erleada) with chemotherapy in early-stage disease.

What are some challenges faced with the AR inhibitors that still need to be addressed?
At this time, it is very difficult to answer that question because we have a very low experience with apalutamide. The 2 agents, enzalutamide and apalutamide, have a very similar molecular structure. The main difference may be in terms of penetration of the blood-brain barrier. There is no other main difference [between the two] in terms of activity. In terms of early-stage disease, it is very difficult to understand the difference in outcomes for patients treated with these two agents.

What does this all mean for patients?
In this moment, we have reached the maximum of results in terms of improvement of prognosis in our patients, especially compared with 2 decades ago. Patients with mCRPC are living longer, but the main problem is that all of our available drugs target the AR, except for radium-223 dichloride (Xofigo). In the future, the main challenge will be to develop new agents that will be able to interact with different targets. Right now, we have several trials with PARP inhibitors and checkpoint inhibitors. We need to find more active targets for new drugs.

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U.S. Leads World in Reducing Prostate Cancer Cases

By Robert Preidt
HealthDay Reporter

TUESDAY, April 2, 2019 (HealthDay News) -- Rates of prostate cancer cases and deaths have declined or stabilized in many countries. And the United States had the largest recent decrease in disease incidence, a new study says.

"Previous studies have indicated significant variation in prostate cancer rates, due to factors including detection practices, availability of treatment, and genetic factors," said study author MaryBeth Freeman. She's a senior associate scientist for surveillance research at the American Cancer Society.

"By comparing rates from different countries, we can assess differences in detection practices and improvements in treatment," Freeman said in a news release from the American Association for Cancer Research (AACR).

Researchers examined long-term and short-term data from 44 countries with incidence data and 71 countries with prostate cancer death data.

Of the 44 countries assessed for incidence, prostate cancer rates rose in four countries and fell in seven, with the United States with the biggest decrease. Rates remained stable in the other 33 countries.

Of the 71 countries assessed for prostate cancer death rates, there were decreases in 14, increases in three, and no change in 54.

As of 2012, prostate cancer was the most commonly diagnosed cancer among men in 96 countries and the leading cause of death in 51 countries, according to the study.

Freeman said the findings confirm the benefits of prostate-specific antigen (PSA) screening. She noted that in the United States, incidence rates rose from the 1980s to the early 1990s, then declined from the mid-2000s through 2015, largely due to increased use of PSA screening.

This type of screening is less available in poorer nations, meaning that men there are more likely to be diagnosed at later stages of prostate cancer and more likely to die, Freeman said.

She noted that some nations plan to scale back recommendations for PSA screening due to fears about possible overtreatment of prostate cancer that would never cause symptoms.

Dr. Eric Horwitz, professor of medicine at Fox Chase Cancer Center in Philadelphia, said this line of thinking is "potentially problematic."

The U.S. Preventive Services Task Force recommends that men aged 55 to 69 undergo periodic screening after they've discussed the risks and benefits with their doctor.

"The screening recommendations were changed recently after further analysis of the U.S. data and we are now seeing more high-risk prostate cancer diagnoses that require treatment," said Horwitz, who wasn't involved with the study.

Freeman said future studies should monitor trends in mortality rates and late-stage disease to assess the impact of reduction in PSA testing in several countries.

The study was to be presented Tuesday at the AACR annual meeting, in Atlanta. Data and conclusions presented at meetings are usually considered preliminary until published in a peer-reviewed medical journal.

WebMD News from HealthDay

Sources
SOURCES: Eric Horwitz, M.D., professor, medicine, Fox Chase Cancer Center, Philadelphia; American Association for Cancer Research, news release, April 2, 2019

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Web tool aims to better inform and refine need for treatment in early prostate cancer

Date: March 12, 2019 Source: University of Cambridge

A new tool to predict an individual’s prognosis following a prostate cancer diagnosis could help prevent unnecessary
treatment and related side effects, say researchers at the University of Cambridge.

The tool, PREDICT Prostate, launches today to coincide with publication in the journal PLOS Medicine of the research that underpins it. It brings together the latest evidence and mathematical models to give a personalised prognosis, which the researchers say will empower patients as they discuss treatment options with their consultant.

According to Cancer Research UK, there were 47,151 new cases of prostate cancer in 2015. Progression of the disease, which usually presents in later life, is very variable: in most cases, the disease progresses slowly and is not fatal. It is often said that more men die with prostate cancer than from it. However, it is still the case that in a significant number of men, the tumour will metastasise and spread to other organs, threatening their health.

When a patient is diagnosed with prostate cancer, they are currently classified as low, intermediate or high risk. Depending on the patient’s risk group, clinicians will recommend either an ‘active monitoring’ approach or treatment. Treatment options include radiotherapy or surgery and can have potentially significant side-effects, including erectile dysfunction and urinary incontinence.

However, evidence suggests that these classifications, which are in the current guidelines provided by the National Institute for Health and Care Excellence (NICE), are only 60-70% accurate. This means that many men may elect for treatment when it is not necessary. In fact, a recent study carried out in the UK showed that for early prostate cancer (low and intermediate risk), treatment is no more beneficial in terms of ten year survival compared to no treatment.

Cambridge researchers have already shown that it is possible to improve the accuracy of the NICE-endorsed model to more than 80% by stratifying patients into five rather than three groups. Their next challenge was to use this information to give a more individual prediction of outcome to patients at no extra cost. The result is PREDICT Prostate.

PREDICT Prostate takes routinely available information including PSA test results, the cancer grade and stage, the proportion of biopsies with cancerous cells, and details about the patient including his age and other illnesses. It then gives a 10-15 year survival estimate. Importantly, the tool also estimates how his chance of survival differs depending on whether he opts for monitoring or treatment, providing context of the likelihood of success of treatment and risk of side effects.

“As far as we are aware, this is the first personalised tool to give an overall survival estimate for men following a prostate cancer diagnosis,” says first author Dr David Thurtle, Academic Clinical Fellow in Urology at the University of Cambridge and Addenbrooke’s Hospital, which is part of Cambridge University Hospital NHS Foundation Trust (CUH).

“PREDICT Prostate is designed for men who are considering whether to choose to monitor or to opt for treatment. This is the choice that faces nearly half of all men who are diagnosed with prostate cancer. We hope it will provide a more accurate and objective estimate to help men reach an informed decision in discussion with their consultant.”

The research was led by Dr Vincent Gnanapragasam, University Lecturer and Honorary Consultant at CUH, and undertaken by Dr Thurtle, both of the Academic Urology Group in Cambridge, and in collaboration with Professor Paul Pharoah of the Department of Cancer Epidemiology.

“We believe this tool could significantly reduce the number of unnecessary -- and potentially harmful -- treatments that patients receive and save the NHS millions every year,” says Dr Gnanapragasam.

“This isn’t about rationing treatments -- it’s about empowering patients and their clinicians to make decisions based on better evidence. In some cases, treatment will be the right option, but in many others, patients will want to weigh up the treatment benefits versus the risks of side effects. It will also show men who do need treatment a realistic estimate of their survival after treatment.”

Data from the National Prostate Cancer Audit has shown that rates of treatment for low risk prostate cancer vary across different hospitals between 2-25%. 'Radical' treatment -- surgery or radiotherapy, for example -- costs on average around £7,000 per patient and treating these men unnecessarily wastes considerable resources as well as causing significant side-effects.

Dr Thurtle and Dr Gnanapragasam have since carried out a randomised study of almost 200 prostate cancer specialists in which they gave some clinicians access to the tool and a series of patient vignettes, while others received the vignettes only. In most cases, the clinician overestimated the risk of the patient dying from the cancer, compared to the estimate given by PREDICT, going on to recommended treatment in many cases and overestimate how successful this treatment would be. When given access to the tool, the clinicians were less likely to recommend treatment in good prognosis cancers.

Dr Gnanapragasam says that the development of PREDICT Prostate has only been possible because of the intactness of records available through Public Health England -- the tool was developed using data from over 10,000 UK men recorded in the East of England. This regional registry, he says, is one of the highest quality and most comprehensive data sets available both in the UK and internationally. The data was then validated externally in a sample of 2,500 prostate cancer patients in Singapore. The web tool was developed in collaboration with the Winton Centre for Risk and Evidence Communication.

The researchers caution that the tool is strongly recommended for use only in consultation with a clinician. It is also not suitable for men with very aggressive disease or who have evidence of disease spread at the time of diagnosis.
How prostate cancer becomes treatment resistant

Date: February 28, 2019  Source: Sanford Burnham Prebys Medical Discovery Institute

Summary:

Scientists have identified how prostate cancer transforms into a deadly treatment-resistant prostate cancer subtype called neuroendocrine prostate cancer (NEPC) following treatment with anti-androgen therapy. Their findings -- which include the metabolic rewiring and the epigenetic alteration that drives this switch -- reveal that an FDA-approved drug holds potential as a NEPC treatment.

The development of effective anti-androgen therapies for prostate cancer is a major scientific advance. However, some men who receive these targeted treatments are more likely to develop a deadly treatment-resistant prostate cancer subtype called neuroendocrine prostate cancer (NEPC). No effective treatment for NEPC exists.

Now, scientists from Sanford Burnham Prebys Medical Discovery Institute (SBP) have identified how prostate cancer transforms into aggressive NEPC following treatment with anti-androgen therapy. Their findings -- which include the metabolic rewiring and the epigenetic alteration that drives this switch -- reveal that an FDA-approved drug holds potential as a NEPC treatment. The research also uncovers new therapeutic avenues that could prevent this transformation from occurring. The study was published in Cancer Cell.

"Acquired treatment resistance is a major concern for every oncologist. Eventually, over enough time, cancer patients who receive a targeted therapy can become resistant to treatment," says Darren Sigal, M.D., an oncologist at Scripps Clinic and Scripps MD Anderson Cancer Center who worked with the scientists on the study. "This study is an important advance that helps us understand why targeted treatments for prostate cancer may promote the development of a more aggressive tumor. These insights could lead to better treatments that help fathers, sons and grandfathers around the world who are fighting prostate cancer."

Prostate cancer is the second-leading cause of cancer death for American men, according to the American Cancer Society. The cancer grows in response to hormones called androgens. Targeted therapies that block these hormones have extended survival for many patients. However, nearly all men eventually develop resistance to these treatments. In 2019, more than 30,000 men in the U.S. are expected to die from prostate cancer.

"Similar to bacteria that gain resistance to antibiotics, tumors can become resistant to anti-cancer drugs by 'remodeling' their environment and developing strategies to evade targeted therapies. As targeted therapies become more potent, putting more stress on tumors, we expect to see drug resistance become more common," says Maria Diaz-Meco, Ph.D., the senior author of the paper and a professor in the Cancer Metabolism and Signaling Networks Program at SBP. "Our study shows that in a form of treatment-resistant prostate cancer, a tumor suppressor gene called protein kinase $\lambda$/iota is downregulated. We subsequently identified metabolic and epigenetic vulnerabilities which are possible routes to prevent treatment resistance from arising."

In the study, the scientists analyzed tissue samples from men with metastatic NEPC, prostate cancer cell lines and a new mouse model of NEPC created by the researchers, to identify the molecular switch that triggers prostate cancer to become treatment-resistant NEPC following targeted treatment. In addition to detecting the downregulation of protein kinase C lambda/iota, the scientists found that the NEPC cells upregulate the synthesis of a metabolite called serine. Because serine is a non-essential amino acid, treatments aimed at blocking serine production may be devised that could impact the tumor with minimal or no effect on the normal cells, thereby reducing potential toxicities. Additionally, the researchers discovered that the cancer cells used a communication pathway called mTORC1/ATF4 to accelerate the synthesis of serine, allowing the tumor to grow faster and to epigenetically switch to the NEPC mode. A protein that regulates the positions of lysosomes, the cell's degradation machinery, was also involved in the tumor's transformation. Together, these tumor characteristics represent novel approaches that could prevent prostate cancer from transforming into NEPC.

A new identity

"NEPC is essentially a new cancer. From what it 'eats' to how it looks, the tumor cells are completely reprogrammed. The tumor even loses the receptor that is targeted by current treatments, which is why it is so difficult to treat," says Jorge Moscat, Ph.D., a study author and director and professor in SBP's Cancer Metabolism and Signaling Networks Program. "Identifying the switch that drives the transformation from prostate cancer to NEPC is a critical first step toward developing treatments that prevent treatment resistance in men with prostate cancer before it begins."
NETWORKING

Please help us in our outreach efforts. Our speakers bureau consisting of Lyle LaRosh, Gene Van Vleet and George Johnson are available to speak to organizations of which you might be a member. Contact Gene 619-890-8447 or gene@ipcs.org to coordinate.

Member and Director, John Tassi is the webmaster of our website and welcomes any suggestions to make our website simple and easy to navigate. Check out the Personal Experiences page and send us your story. Go to: https://ipcs.org/personal-experience

Our brochure provides the group philosophy and explains our goals. Copies may be obtained at our meetings. Please pass them along to friends and contacts.

FINANCES

We want to thank those of you who have made special donations to IPCSG. Remember that your gifts are tax deductible because we are a 501(c)(3) non-profit organization.

We again are reminding our members and friends to consider giving a large financial contribution to the IPCSG. This can include estate giving as well as giving in memory of a loved one. You can also have a distribution from your IRA made to our account. We need your support. We will, in turn, make contributions from our group to Prostate Cancer researchers and other groups as appropriate for a non-profit organization. Our group ID number is 54-2141691. Corporate donors are welcome!

If you have the internet you can contribute easily by going to our website, http://ipcs.org and clicking on “Donate”. Follow the instructions on that page. OR just mail a check to: IPCSG, P. O. Box 4201042, San Diego CA 92142

Directions to Sanford-Burnham-Prebys Auditorium

10905 Road to the Cure, San Diego, CA 92121

Take I-5 (north or south) to the Genesee exit (west).

Follow Genesee up the hill, staying right.

Genesee rounds right onto North Torrey Pines Road.

Do not turn into the Sanford-Burnham-Prebys Medical Discovery Institute or Fishman Auditorium

Turn right on Science Park Road. Watch for our sign here.

Turn Left on Torreyana Road. Watch for our sign here.

Turn Right on Road to the Cure (formerly Altman Row). Watch for our sign here.