

Cancer Advances

Cleveland Clinic Cancer Center | Winter 2018

TLR4:

The **Key** to
Cancer Stem Cell
Evasion of Immune
Suppression?

Dear colleagues,

Welcome to the latest edition of *Cancer Advances*. Few things fill me with more personal pride than reviewing the work described in these pages. The work highlighted here is the result of dozens of talented clinicians and researchers working together to advance diagnostics and treatments for the patients we serve.

The lab of Justin Lathia, PhD, is on a mission to disrupt cancer stem cell-driven resistance and growth in various malignancies. The research moves us closer than ever to an understanding of this model of tumorigenesis. The lab of Yogen Sauntharajah, MD, has identified a genetic alteration key to the development of liver cancer. Another genetic variant offers clues to thyroid cancer predisposition in the work of Charis Eng, MD, PhD.

From using molecular and genetic clues to drive discovery to testing novel therapeutics, combinations and regimens, our breakthroughs are reshaping the treatment landscape for many diseases, including refractory acute myeloid leukemia. Radiation oncologist Jacob Scott, MD, is studying the role drug holidays might play in reducing acquired resistance and making our current therapeutics more effective. Jame Abraham, MD, is similarly focused on using existing therapies to enhance outcomes, with a new combination therapy for advanced HER2+ breast cancer.

Our continued advances and leadership in radiation oncology are reflected in a new, safe and effective modality for treating large brain metastases and in the pivotal role of Gregory Videtic, MD, in creating ASTRO's new SBRT guidelines.

The sheer breadth, depth and impact of this work remind me of the enormous scope of our ultimate goal: to offer the best care possible to patients with myriad and difficult diseases. I hope in these pages you find inspiration for your own work, and please contact me with any questions, concerns or suggestions.

Sincerely,

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TLR4: The Key to Cancer Stem Cell Evasion of Immune Suppression?

The cancer stem cell (CSC) model of tumorigenesis and therapeutic resistance is a fairly recent but important development in oncologic research. Justin Lathia, PhD, and his lab are driving this model forward with their discovery of how CSCs evade the immune system.

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Cover image: Fluorescent cancer stem cells engineered for tracking cell-to-cell interactions.

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Though experimental evidence has shown that CSCs drive many advanced cancers, researchers have until now not understood how they evade the immune system.

The work of Dr. Lathia, a stem-cell biologist at Cleveland Clinic's Lerner Research Institute, brings us closer than ever to this understanding. With funds from multiple NIH grants (including two R01s), Case Comprehensive Cancer Center, the American Cancer Society and VeloSano, Dr. Lathia and his team hope to exploit their lab's findings to disrupt CSC-driven resistance and growth in various malignancies.

Glioblastoma CSCs express less TLR4

Dr. Lathia's latest research focuses on how CSCs thrive in the glioblastoma (GB) tumor microenvironment. Marked by hypoxia, acidic stress and necrosis, this toxic environment, a byproduct of the rapid and uncontrolled proliferation of cancer cells, is hostile to most cell types — except CSCs.

This exception intrigued Dr. Lathia and his colleagues. What do CSCs have that other cells don't? Their recent publication in *Cell Stem Cell* provides an answer.

"We saw two concepts at odds with each other,"

Dr. Lathia says of this research funded by Blast Glioblastoma, B*CURED, VeloSano and the Sontag Foundation. "One concept is that one of the hallmarks of advanced cancers is areas of necrosis ... where the tissue runs out of nutrients and is highly stressed and the cells just die, and they emit their contents into the extracellular space.

"The other concept is that cells have evolved mechanisms to sense such damage, so if there's an injury and a bunch of cells die in a given organ, that organ has the ability, even before the immune system responds, to sense the damage and respond to it. So how do cancer stem cells continue to persist? That was the central question of the paper."

Through a side-by-side comparison of CSC and non-CSC reactions in specific toll-like receptor (TLR) cultures, Dr. Lathia and his co-authors found that CSCs in GB have adapted to express a lower level of the innate TLR4, the receptor that activates an immune response (Figure). These diminished TLR4 levels allow the CSCs to

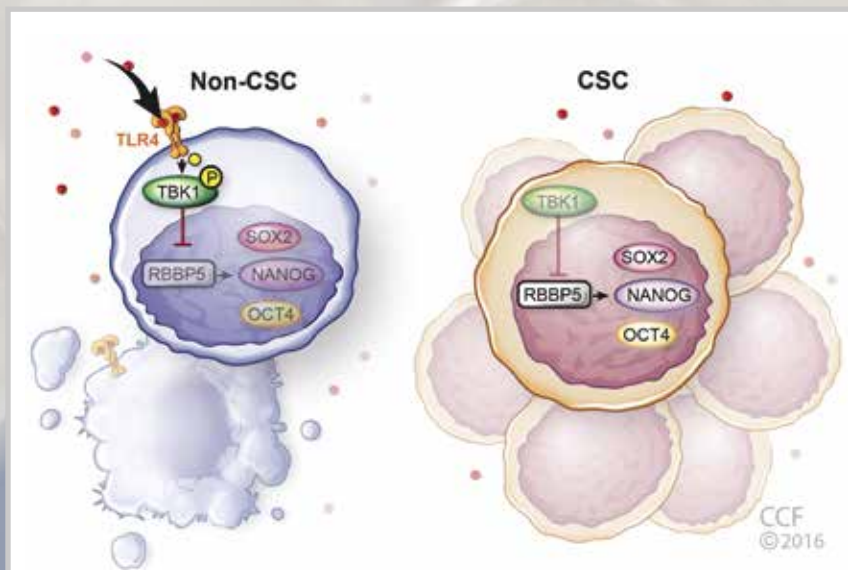


Figure. Model summarizing the role of TLR4 in glioblastoma. Non-CSCs possess TLR4, which can sense damage signals in the tumor microenvironment and suppress stem cell signaling via inhibition of RBBP5. CSCs, however, have low TLR4 expression, which allows them to persist and expand despite damage signals in the tumor microenvironment.

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persist and multiply, repopulating a tumor in a hostile microenvironment.

“It’s like CSCs have their headphones on and have lost the ability to sense the environment around them,” says Dr. Lathia. “This is an evolutionary advantage that allows them to grow and persist, despite being damaged in the surrounding microenvironment.

“What really jumped out at us was if you put TLR4 ligands on cancer cells that are non-CSCs, those cells die. They really don’t like being cultured with TLR4 ligands, but the CSCs just don’t care,” Dr. Lathia says. “You can put any ligand you want on a cell, and the cell is only going to respond if it has the corresponding receptor. We screened all toll-like receptors and found that CSCs had a very low level of TLR4.” The team then tested its findings by engineering CSCs with a higher level of TLR4. The result? The CSCs grew more slowly and lost their stem cell characteristics.

Knowing that it would be difficult to restore TLR4 receptors to CSCs, Dr. Lathia’s team looked downstream of the protein and found the transcription factor retinoblastoma-binding protein 5 (RBBP5), which has an inverse relationship with TLR4. Using RNA interference, they reduced the levels of RBBP5 in GB cells and found the CSCs didn’t grow or self-renew as well as before. They also discovered that RBBP5 is part of the epigenetic complex that ensures CSC transcription factors remain activated. Thus, if RBBP5 is suppressed, Dr. Lathia reasoned, CSCs might not replicate.

“We were basically able to map out a signaling pathway that starts with TLR4 and involves RBBP5 and the core stem cell circuitry,” he says. “The reason this is important is this is one of the first examples of an immune signaling response directly interacting with the stem cell circuitry.”

The therapeutic answer might seem obvious — inject GB patients’ tumors with TLR4. In fact, this type of approach is being used in some clinical trials involving other toll-like receptors and other types of cancers. Dr. Lathia, however, has concerns. He hypothesizes that such an approach might change the dynamics of the tumor, killing all the non-CSCs but leaving behind a plethora of CSCs. His lab is currently investigating this approach, adding TLR4 ligands to GB cells in preclinical

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Lathia and Reizes Labs Find CD55 Key to Endometrial Cancer Recurrence and Resistance

The research teams of Justin Lathia, PhD, and Ofer Reizes, PhD, recently discovered a key pathway that leads to recurrence and treatment resistance in endometrial cancer.

For the past 25 years, standard therapy for endometrial and ovarian cancers has included surgery and cisplatin. After an initial response, the cancer often recurs and becomes resistant to cisplatin, leaving patients with limited treatment options.

The Cleveland Clinic team studied the unique role of CD55, which is abundant on the surface of endometrioid ovarian cancer and uterine cancer cells. Using human cells and patient-derived tissue models, they found CD55 to be the most prevalent on cancer stem cells (CSCs).

The researchers discovered that high levels of CD55 caused CSCs to be more aggressive and resistant to cisplatin than non-CSCs. The CD55 pathway is unique in that it controls both self-regulation and therapeutic resistance.

In addition, when CD55 was removed from cells, the cells became sensitive to cisplatin in cell culture models and in preclinical mouse models. The researchers hope that blocking the protein will enhance cisplatin treatments and that high expression of CD55 could be used as a biomarker of aggressive gynecologic cancers. The team plans to complete further preclinical testing followed by a clinical trial in patients with CD55-expressing endometrial cancers.

Drs. Lathia and Reizes, both of the Department of Cellular and Molecular Medicine at Cleveland Clinic Lerner Research Institute, co-led the study. Dr. Reizes holds the Laura J. Fogarty Endowed Chair for Uterine Cancer Research at Cleveland Clinic.

“We have discovered a unique role for the CD55 complement signaling pathway in cancer as a target, which offers an opportunity to prevent recurrence and associated mortality. Fortunately, there is already an FDA investigational drug that can inhibit the CD55 signaling pathway,” Dr. Lathia says. “We hypothesize that using this drug in combination with cisplatin will improve treatment outcomes.”

“Endometrial cancer is the most common gynecologic malignancy in the United States, yet research in this area is understudied and underfunded,” Dr. Reizes adds. “We hope that our study will lead to much-needed new therapy options for women with treatment-resistant relapsed disease.”

Research fellow Caner Saygin, MD, was first author on this study, which was published in the *Journal of Experimental Medicine*.

This work is funded by NIH grant CA191263. This work utilized the Leica SP8 confocal microscope that was purchased through NIH SIG grant 1S100D019972-01.

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mouse models to see whether such therapies could be a long-term solution for patients.

Other avenues: cell-to-cell communication, high-throughput screening and MDSCs

In addition to its work on TLR4, Dr. Lathia's team is exploring the questions of CSC-driven tumor progression and therapeutic resistance from many angles. One angle is cell-to-cell communication — specifically a class of cell surface channels called connexins that form gap junctions and directly connect the cytoplasm of the two cells. Gap junctions can rapidly and efficiently pass cargo — molecules, ions and electrical impulses — between cells. The team has shown that specific connexin channels in GB and breast cancer can accelerate tumor growth. They are now researching the signaling process to understand how that happens and have also leveraged this work to include prostate cancer and leukemia.

The lab is also using high-throughput screening to sift through more than 800 FDA-approved compounds to find those that might inhibit this particular cell-to-cell communication. They have found 10 and, so far, have shown one will extend survival in tumor-bearing mice models. They plan to chemically modify these parent compounds to make new drugs that will inhibit cell-to-cell communication between malignant cells.

Dr. Lathia's lab is also pursuing how to shift the balance in the immune system to better fight brain cancer. Certain cancers such as GB accumulate myeloid-derived suppressor cells (MDSCs) that suppress the immune system. In tumor cells, however, MDSCs can also suppress cytotoxic T cells, rendering them impotent.

To flip that scenario, Dr. Lathia and Cleveland Clinic colleagues David Peereboom, MD, Director of Clinical Research at Cleveland Clinic's Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center, and Michael Vogelbaum, MD, PhD, Associate Director of the Neuro-Oncology Center, are conducting a phase 1 clinical trial that attempts to target MDSCs in recurrent GB patients using low-dose chemotherapy.

"We're trying to inverse the immune suppression, to inhibit the inhibitors," Dr. Lathia says. "We've tried it in myriad ways, but one blunt way is just by giving patients low-dose chemotherapy such as 5-fluorouracil, which has been around for decades. If you give it twentyfold less than traditionally used for a cancer patient, you can actually target the MDSCs."

The low dose, which exploits MDSCs' relative sensitivity to chemotherapy, safeguards the cytotoxic T cells. "In a 2016 paper in *Stem Cell*, we showed that increasing the dose of 5-fluorouracil high enough can kill cytotoxic T cells as well, which we don't want to do. But there's a sweet spot, a therapeutic window that we think we have found."

Dr. Lathia's lab has active projects in cell adhesion mechanisms, cell-cell communication and the interaction between tumor cells and the immune system. "Our next step is developing new methods to track the stem cell state in real time and single-cell cell-fate decisions," says Dr. Lathia. "This should bring us closer to fully understanding and thus being able to disrupt the process."



Enasidenib Effective Treatment for Refractory Acute Myeloid Leukemia

Precision therapy for refractory disease

The FDA approval of enasidenib for the treatment of IDH2-mutated relapsed/refractory acute myeloid leukemia (AML) marks a new era for patients who previously had few options, says Mikkael Sekeres, MD, MS, Director of Cleveland Clinic Cancer Center's Leukemia Program and site leader for clinical trials testing the drug.

The precision therapy inhibits the mutation of the IDH2 protein that blocks myeloid differentiation, which occurs in about 12 percent of patients with AML. Enasidenib at doses of 50 to 650 mg daily produced an overall response rate (ORR) of 40.3 percent (95% CI, 33-48) and a 19.3 percent (95% CI, 13.8-25.9) rate of complete remission (CR), according to results from a phase 1/2 clinical trial recently published in *Blood*.

"For many decades, we've only had limited advances in the treatment of refractory AML, and five-year survival for these patients was in the single digits," says Dr. Sekeres. "Enasidenib reshapes the treatment landscape; it induces durable complete remissions and extends survival benefit substantially."

Increased OS, if clinicians are patient

The two-part study included dose-escalation and dose-expansion cohorts to test the maximum tolerable dose, pharmacologic profiles and safety for all patients

(N = 239). Patients received five dose levels (30, 50, 75, 100, 150 mg) twice daily for 28 days and eight dose levels (50, 75, 100, 150, 200, 300, 450, 650 mg) once daily for 28 days in the dose-escalation phase.

Clinical efficacy was assessed for patients with relapsed/refractory disease (N = 176), and results for this group show a median overall survival (OS) of 9.3 months, and 19.7 months for patients who reached CR.

Adverse events were generally tolerable, with grade 3/4 events including hyperbilirubinemia (12 percent), thrombocytopenia (6 percent) and anemia (5 percent).

Because enasidenib works by inducing myeloblast differentiation, first response is a bit delayed compared with cytotoxic therapies. "Patience is key," says Dr. Sekeres. "Our results show that it takes about two months to show a response and about four months to complete response. We need to give the therapy time to work, because the payoff can be significant."

Further trials are planned or underway at Cleveland Clinic and other sites to compare enasidenib with conventional treatments for older patients with relapsed/refractory AML, to establish optimal dosing, and to expand the treatment to other disorders such as myelodysplastic syndrome.

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Two-Staged Stereotactic Radiosurgery for Large Brain Metastases

Growing evidence of advantages over other radiosurgery approaches from the largest series to date

By Lilyana Angelov, MD; Samuel Chao, MD; and Gene Barnett, MD, MBA

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Two-staged stereotactic radiosurgery has been shown to be a feasible, safe and effective modality for treating large brain metastases, in the largest published series of metastases managed with this approach to date. These results, reported recently by our group in the *Journal of Neurosurgery*, raise the prospect of enhanced local tumor control with decreased radiation-related morbidity in the setting of large brain metastases.

The rationale for staged therapy

Effective control of large brain metastases (≥ 2 cm maximum diameter) with stereotactic radiosurgery (SRS) is a challenge, yielding local control rates of only 37 to 62 percent with an elevated risk of treatment-associated toxicity compared with similar treatments for smaller brain metastases. In recent years, two centers in Japan began reporting results with a novel strategy for treating large brain metastases known as staged stereotactic radiosurgery (SSRS).¹⁻³ The approach involves delivery of SRS in two or more discrete treatment sessions rather than the traditional single session. The aim is to enable an increased overall dose to improve local tumor control while administering smaller individual doses in an effort to reduce toxicity.

In 2012, Cleveland Clinic's Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center became, to our knowledge, the first center outside Japan to offer two-staged SRS (2-SSRS). Our new paper reports our experience with this approach from June 2012 through January 2016.

Our study in brief

We retrospectively analyzed all Cleveland Clinic patients during this period who underwent planned 2-SSRS for brain metastases ≥ 2 cm in maximum diameter secondary to systemic cancer. Patients were selected for planned 2-SSRS if they were not surgical candidates, or per surgeon and patient preference. The Gamma Knife® Perfexion™ system was used to deliver a total of 24 to 33 Gy (median, 30) across the two treatment sessions,

resulting in a total biologic equivalent prescription dose of roughly 44 to 73 Gy (median, 62.5) if delivered in a single treatment session. The second SSRS session was typically scheduled approximately one month after the first (median interval, 34 days).

Our objective was to volumetrically assess the response of local brain metastases to the 2-SSRS strategy in terms of local control rates, treatment-related toxicity and impact on overall survival.

Key results

Fifty-four patients received 2-SSRS during the study period, with a total of 63 treated brain metastases among them: 46 patients (85 percent) had one metastasis, seven (13 percent) had two and one (2 percent) had three. Patients with more than one metastasis had them treated concurrently. Median patient age was 63 years (range, 23-83).

The main outcome findings were as follows:

- The median change in tumor volume at three-month follow-up MRI after 2-SSRS was a 54 percent reduction from baseline ($P < .001$). (See Figure for an example case.)
- Rates of local control were 95 percent at three months and 88 percent at six months.
- Estimated overall survival rates (using the Kaplan-Meier method) were 65 ± 7 percent at six months and 49 ± 8 percent at 12 months.
- Seven lesions (11.1 percent) demonstrated adverse radiation effects (four lesions at grade 1/2 toxicity and three at grade 3).
- Nine lesions (14.3 percent) demonstrated local progression (median time, 5.2 months). Reduced time to progression was significantly associated with greater tumor size at baseline and smaller absolute and relative reductions in tumor volume from baseline to the second SSRS session.

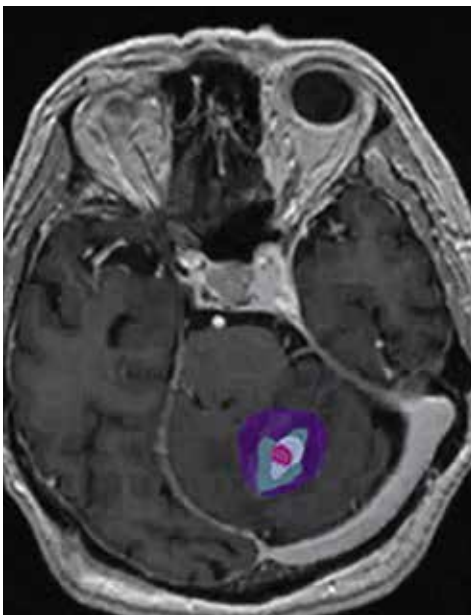


Figure. Tumor size over time in one of the patients from our study. Image courtesy of neurosurgery resident Ghaith Habboub, MD.

- Pre 2-SSRS stage 1 ● 3-month follow-up
- Pre 2-SSRS stage 2 ● 6-month follow-up

Time for a prognostic model?

Our findings build on the initial results from Japan to support 2-SSRS as a feasible, safe and effective modality that yields excellent local control and similar or better overall survival and toxicity relative to many series (reviewed in our paper) in which large brain metastases were treated with single-session SRS or fractionated stereotactic radiosurgery (FSRS). We also showed that multiple large brain metastases can be treated concurrently with 2-SSRS and that this strategy can be effective in treating large metastases arising from traditionally radiotherapy-resistant pathology.

These findings suggest that a prognostic model may well be in order to stratify patients with large brain metastases into favorable and unfavorable 2-SSRS response groups based on Karnofsky Performance Status, global intracranial disease and response of the tumor to initial SSRS treatment. Such a model could be a helpful guide in clinical decision-making.

Potential advantages and applications

At the same time, larger prospective trials are warranted to confirm these retrospective results, assess durability and directly compare 2-SSRS to alternative approaches for large brain metastases. Nevertheless, 2-SSRS appears to offer a number of advantages over other radiosurgery strategies in the setting of large brain metastases, including:

Some of the best survival data to date. As reviewed in our paper, median survival in our study exceeded that of six of seven SRS cohorts with data from the published literature and exceeded that of seven of 12 FSRS studies with data from the literature. Twelve-month survival in our study surpassed that of four of five single-fraction studies and six of 11 FSRS studies with data from the literature.

Convenience. Use of 2-SSRS is independent of delivery platform (in contrast to the current limitation of FSRS to frame-based platforms) and may be the least disruptive treatment approach in terms of the patient's overall care regimen.

Possible radiobiological advantages. These include the potential for enhanced tumor kill through higher doses per session relative to FSRS, the potential for repair and repopulation of normal brain cells between the first and second sessions, and the prospect of improved oxygenation to the remaining tumor cells — and thus enhanced radiation sensitivity — resulting from decreased tumor size following the first session.

Apart from these broader potential advantages, 2-SSRS appears particularly well-suited to several specific applications. These include treating tumors in eloquent brain or near critical structures where radiotoxicity is especially concerning, enabling deferral of whole-brain radiation therapy (WBRT) in patients who aren't surgical candidates, and use in patients with limited options who have already had WBRT and are not surgical candidates. We look forward to helping further define the role of this promising new approach to stereotactic radiosurgery.

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A New Strategy for Cancer Treatments

A dynamic approach to an evolving disease

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Jacob Scott, MD, thinks we may already have all the drugs we need to treat most cancers. We just need to be smarter about how we use them.

That's a bold statement, considering entire divisions of academic medical centers are devoted to novel therapeutics and drug development, and the global cancer drug market is expected to balloon by 50 percent from about \$80 billion this year to \$120 billion by 2020.

Then again, consider that many new targeted therapies measure success based on months of additional survivorship — not years or decades. And some of the most difficult cancers invariably acquire resistance to designer biologics of molecular precision.

"The fundamental problem of targeted therapies is that cancer is a disease of evolution," says Dr. Scott, a physician-scientist in the Department of Translational Hematology and Oncology Research at Cleveland Clinic. "Tumors are dynamic organisms that adapt rapidly and ruthlessly to their environments — it's survival of the fittest in the tumor environment, and when the fittest means the least likely to respond to chemotherapy, that inevitably leads to drug resistance and eventually a need for new treatment."

In short, when a targeted therapy destroys most of a tumor, some of it survives. As it recovers, it propagates from cells that didn't respond to treatment during the first course. Each cell also has its own constellation

of mutations and molecular alterations. After several courses of different therapies, the result can be a tangled mess of invasive tissue with a vexing and resilient mutational landscape.

That may sound bleak, but Dr. Scott doesn't think so — at least not if we look at cancer through the lens of long-term strategy rather than short-term gains.

"I'm a hopeless optimist," says Dr. Scott. "If we can shift our thinking away from a step-by-step approach toward a more strategic game, I believe we can make some significant improvements in our approach to precision medicine."

From short-term gains to long-term strategy

Dr. Scott and a growing number of like-minded cancer researchers are leading the charge in this refined approach to cancer research.

"We've been playing whack-a-mole with cancer for the past 40 years," says Dr. Scott. "We can hit them faster and with more accuracy now than we could in 1977, but no matter how many we knock down, another invariably pops up." New strategies more closely resemble a game of chess.

To test the viability of this approach, Dr. Scott and collaborators at the University of Oxford and Moffitt Cancer Center started with a notoriously resilient cancer, ALK-mutated non-small-cell lung cancer (NSCLC).



Through repeated exposure to ALK-targeted therapies, the team conditioned a series of independent NSCLC cell lines to acquire drug resistance.

They then began experimenting with drug holidays (or treatment interruptions) of varying intervals and eventually ALK-targeted therapies after a battery of chemotherapies that are generally considered inferior as first-line treatments.

Drug holidays and acquired resistance

Results of the study were published recently in *Nature Scientific Reports* and are among the first to address the combined dynamic of drug holidays and acquired resistance.

Study results show that cancers resistant to ALK-targeted treatments often respond better after exposure to collateral drugs and radiation generally considered inappropriate for first-line therapy.

The collateral drugs appeared to affect the cancers in such a way as to take advantage of a weakness that had once been inaccessible because of tumor evolution.

“The observations and method of understanding drug sequencing presented here represent a novel way to utilize existing drugs to regain the upper hand in the clinics against drug resistance, without the need for costly new drugs,” the team wrote.

Like a chess grandmaster baiting opponents into exposing weaknesses, researchers are using drug resistance patterns as a way to strategize treatment.

“The end goal of our research is to understand and predict the changes tumors experience during treatment so we can better plan second-line therapy when the unavoidable drug failures occur,” says Dr. Scott. “However, collateral sensitivity is highly dynamic and truly represents a moving target.”

There is no average

Further study of this approach is necessary before such practice becomes routine. And the profound complexity of tumor heterogeneity will continue to pose hurdles for individual practitioners.

However, no two cancers are the same. They evolve and adapt rapidly, and they do so differently in every patient. Why should we treat the average when no such thing exists?

“Researchers have known that avoiding cross-resistance is key; this investigation tells us we also need to start considering drug holidays as well,” said Dr. Scott. “We hope our work informs future similar studies across a variety of cancer types, and eventually results in more tailored treatment plans for patients.”

A Promising New Combination Therapy for **Advanced HER2+ Breast Cancer**

Women with advanced HER2-positive breast cancer have several treatment options, but a large number of patients still die from this aggressive form of breast cancer.



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A combination therapy of two promising drugs, however, offers hope of stopping disease progression in some while slowing it for others.

Preliminary results of NSABP FB-10, the dose-escalation trial of neratinib with trastuzumab emtansine (T-DM1) combination therapy, showed response from more than half of women with advanced HER2-positive breast cancer who had developed resistance to trastuzumab and pertuzumab. Some experienced complete response for nearly 18 months.

“Our hope is this combination will provide another highly active regimen for women with metastatic HER2-positive breast cancer that could increase the chances of response and extend survival,” says Jame Abraham, MD, Director of the Breast Oncology Program at Cleveland Clinic Cancer Center. Alberto Montero, MD, MBA, staff in the Department of Solid Tumor Oncology, was a co-author. Dr. Abraham presented the findings at the 2017 American Association for Cancer Research Annual Meeting in Washington, D.C.

A total of 22 patients were enrolled in this phase 1b dose-escalation trial. For the 16 patients who were evaluable for efficacy, the objective response rate was 56 percent. Efficacy results showed that three patients had a complete response, lasting 17.1 months, 11.9 months and 12 months; six patients had a partial response; three patients had stable disease; and four patients had progressive disease.

New drug combination, new hope

The drugs' mechanisms of action appear to have synergistic effects in cases of advanced HER2-positive breast cancer. As monotherapy, both agents have been shown to overcome common resistance to trastuzumab alone in HER2-positive breast cancer patients.

T-DM1 is a conjugated antibody that targets the extracellular domain of HER2. With T-DM1, trastuzumab is armed to deliver the potent cytotoxic payload of DM1, a maytansinoid antimicrotubule agent, selectively to antigen-expressing HER2-positive cells.

Neratinib, on the other hand, targets tumors from within the cell. It is an irreversible tyrosine kinase inhibitor (TKI) that interrupts signaling across the ErbB family by inhibiting phosphorylation and activity of HER2, as well as epidermal growth factor receptors HER1 and HER4. The FDA recently approved neratinib for extended adjuvant treatment of HER2-positive breast cancer.



Potent and well-tolerated

Major side effects of the combination included diarrhea and nausea, which Dr. Abraham and his collaborators intend to treat prophylactically during an ongoing phase 2 trial.

“Side effects from this therapy appear to be manageable with antidiarrheal and anti-nausea medications, which is something we consider promising for the future of this regimen,” says Dr. Abraham.

Patients in the study all had metastatic HER2-positive breast cancer with prior trastuzumab and pertuzumab treatment. None of the participants had previous therapy with T-DM1 or any HER2 TKIs, persistent grade 3 or higher diarrhea, symptomatic brain metastases, active hepatitis or other conditions significantly affecting gastrointestinal function.

Dr. Abraham and his collaborators are currently recruiting about 60 women for a phase 2 trial to demonstrate efficacy.



News Brief

Navneet Majhail, MD, MS, has been awarded an R01 grant from the National Cancer Institute to study the efficacy of an online and phone-based self-management program for hematopoietic cell transplant (HCT) survivors. HCT survivors experience high rates of late mortality, life-threatening chronic health conditions and emotional distress. The award of \$3.6 million over five years will support a clinical trial among 13 national transplant programs and will test whether a personalized web-based intervention can enhance adherence to preventive care and improve emotional distress in adult transplant survivors with hematologic malignancies.

Dr. Majhail is Director of Cleveland Clinic's Blood and Marrow Transplant Program and a Professor of Medicine at Cleveland Clinic Lerner College of Medicine. He serves as co-principal investigator on this project with Karen Syrjala, PhD, and K. Scott Baker, MD, MS, from the Fred Hutchinson Cancer Research Center in Seattle.

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ASTRO's New SBRT Guidelines:

Thoughts from the Task Force Co-Chair

Dr. Videtic is Section Head for Thoracic Malignancies and Residency Program Director in the Department of Radiation Oncology, and Professor at Cleveland Clinic Lerner College of Medicine. He can be reached at videtig@ccf.org or 216.444.9797.

The new guidelines from the American Society for Radiation Oncology (ASTRO) on the use of stereotactic body radiation therapy (SBRT) in early-stage non-small-cell lung cancer (NSCLC) specifically address use for complex or high-risk patients who are not surgical candidates, says task force co-chair and Cleveland Clinic radiation oncologist Gregory Videtic, MD.

SBRT is an advanced type of external beam radiation therapy that uses sophisticated planning techniques to deliver high doses precisely to a tumor. "With SBRT, the radiation oncologist is acting like a sniper, zeroing in on the mass and destroying it with high doses of radiation," explains Dr. Videtic, Section Head for Thoracic Malignancies in the Department of Radiation Oncology. This precision makes SBRT notably effective at sparing healthy tissues surrounding the tumor, which is particularly important in lung cancer.

Over the past 15 years, SBRT has proved to be a tremendous benefit for patients with potentially curable early lung cancers who were not fit for surgery and who historically would have had few options for cure. "We see excellent results in terms of cancer control, and short- and long-term side effects tend to be minimal in this vulnerable population," Dr. Videtic says.

"However," he adds, "there are specific clinical situations that make using SBRT more complex and challenging. So the idea of the new guideline wasn't simply to give a summary of how to approach the standard patient; instead, it was designed to describe those rare, tough scenarios in which the radiation oncologist might wonder whether SBRT is appropriate and safe."

Dr. Videtic was co-chair of the guideline task force, which included both radiation oncologists and surgical oncologists and

drew data from retrospective and prospective studies and the available randomized clinical trials to provide evidence-based recommendations. The document is available in *Practical Radiation Oncology*, ASTRO's clinical practice journal.

Identifying the complex

The conventional SBRT patient has a small lung tissue tumor located away from sensitive organs like the spinal cord, the esophagus and the airways. Some tumors might also lie against the rib cage. Although not complicated to treat, patients with these tumors have a modest chance of scarring in the ribs that might cause irritation in the nerves or a break in the ribs. These symptoms will improve with time as the body continues to heal.

Complex cases, however, include patients whose tumors lie closer to the middle of the chest. The guideline provides a detailed review on how to approach these central tumors with SBRT that considers factors such as tumor relationship to normal structures, previous treatments or tumor size issues. The new guideline also addresses several high-risk clinical scenarios:

- Patients with tumors larger than 5 cm
- Patients with tumors invading the rib cage
- Patients with more than one tumor in one or both lungs at the same or different times
- Patients with a lung removed and with cancer in the remaining lung
- Patients previously treated with surgery, standard radiotherapy or SBRT and whose cancer has recurred

SBRT not first line for surgery-eligible patients

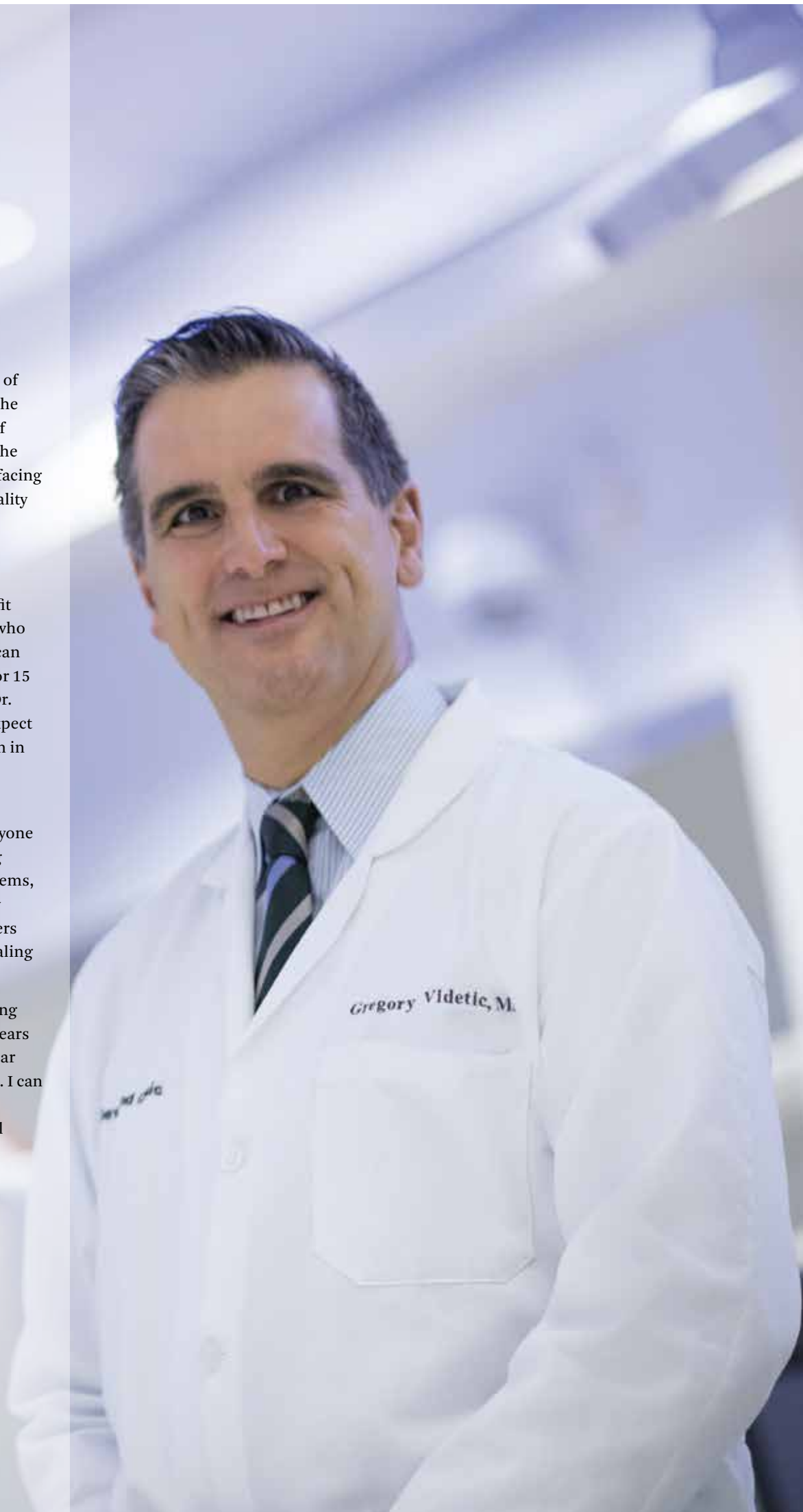
The guideline focuses on patients for whom surgery is not feasible. Because of SBRT's growing popularity, however, the authors also addressed the question of SBRT in patients eligible for surgery. The recommended treatment for patients facing standard risks of surgery-related mortality remains lobectomy with systematic mediastinal lymph node evaluation.

That's because evidence is currently lacking regarding the long-term benefit of SBRT versus surgery. "For patients who potentially have a long life ahead, we can tell them that in the short term — 10 or 15 years — SBRT does a good job," says Dr. Videtic, "but we don't know what to expect for that patient 20 or 30 years out, both in terms of cancer control and safety."

Work in progress as data amasses

The new guideline is a resource for anyone involved in the care of early-stage lung cancer with challenging clinical problems, says Dr. Videtic, and may be especially helpful for physicians in smaller centers with less SBRT experience who are dealing with high-risk patients.

"Most of the data that come from treating lung cancer patients take at least five years to accumulate," he says. "This particular guideline and the data in it reflect that. I can imagine that every three to five years, as more data comes, this guideline will get updated."



Research Team Identifies **GATA4** Loss of Function as **Oncogenic** in Hepatocellular Carcinoma

Cleveland Clinic Cancer Center and the National Cancer Center of Singapore have identified a genetic alteration that plays a central role in the development of liver cancer and may lead to effective new treatments.

By Yogen Sauntharajah, MD

Dr. Sauntharajah co-leads the Developmental Therapeutics Program of the Case Comprehensive Cancer Center, and is staff in the Department of Hematologic Oncology and Blood Disorders at Cleveland Clinic Cancer Center and Professor of Medicine at Cleveland Clinic Lerner College of Medicine.

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Over the past decade, rates of hepatocellular carcinoma (HCC) have been steadily rising, and the prognosis has remained poor. It is the second leading cause of cancer death worldwide, with a five-year U.S. survival rate of 17.6 percent. Risk factors for HCC include hepatitis B virus (HBV) and hepatitis C virus (HCV) infection, diabetes, obesity and alcohol abuse.

Progress in developing new treatments has been slow. The FDA recently approved the first new medication in a decade, regorafenib, one of two kinase inhibitors that are the only approved drugs to be exclusively approved for liver cancer. A lack of understanding of the mechanisms that cause the disease has stymied drug development.

Narrowing the gene pool

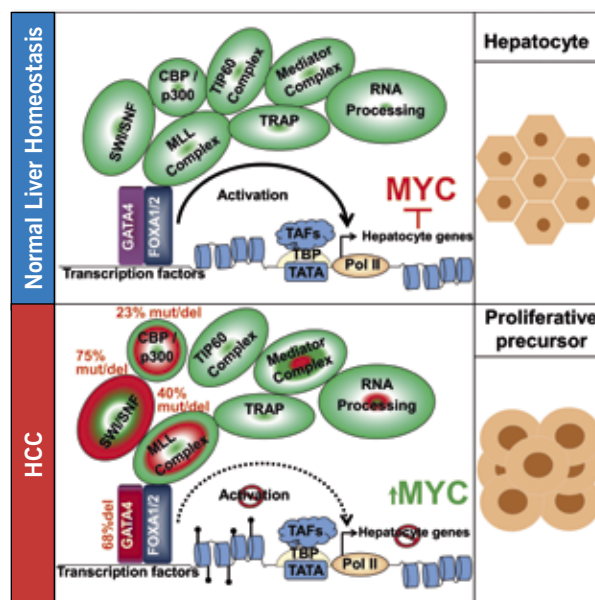
Recent advances in genomic research technologies have enabled major progress in probing the genetic mutations present in HCC cells, increasing the prospects for understanding the molecular mechanisms of HCC oncogenesis. One major discovery was made in the eighth pair of chromosomes (8p) of HCC cells. One of this pair of chromosomes consistently loses about 500 of its genes, a deletion of the short arm of the chromosome found in about 60 percent of liver cancers. This 8p deletion is also found in many other cancers, including lung, colon, breast, bladder, brain, ovarian and prostate.

Of the 500 genes on this chromosome arm, none are mutated at a high rate, the usual way that we identify a gene central to oncogenesis. The discovery of some liver cancer patients with smaller deletions of chromosome 8 narrowed this search, allowing us to target tens instead

Figure. The model: Several genetic alterations in HCC impair master transcription factor-mediated (*GATA4*) chromatin remodeling/transactivation to suppress precursor-to-epithelial transition.

Normal liver cells have intact master transcription factors (e.g., *GATA4*/*FOXA1*) that dictate cell fate by recruiting coactivators (e.g., *ARID1A*) to remodel and activate downstream transcription factors and hundreds of hepatocyte epithelial-differentiation genes, antagonizing *MYC* in the process for terminal epithelial differentiation. In HCC, haploinsufficiency or loss-of-function mutation in one allele of *GATA4* and/or inactivation of *GATA4* coactivators (e.g., *ARID1A*) impairs this chromatin remodeling and transcription activation to produce a selective suppression of terminal epithelial-differentiation genes, a selective repression that is facilitated by the inherently closed chromatin state of these versus commitment and *MYC* proliferation genes.

Figure and caption republished with permission from *The American Society for Clinical Investigation*.





of hundreds of genes. By careful analysis of this shorter list of genes, our research team identified *GATA4* as the key gene, since it is a major transcription factor driver of hepatocyte epithelial lineage fate. Our findings appear in the *Journal of Clinical Investigation*.

When a hepatocyte is missing one copy of *GATA4*, it begins to develop but fails hepatocyte-epithelial differentiation. This is because *GATA4* loss of function favors enzymes that silence rather than activate the genes needed for differentiation. So the precursor cell continues to replicate, in a vain attempt to produce fully formed hepatocytes, resulting in tumorigenesis.

***GATA4* a way forward**

This discovery has major significance for treating liver cancer. Most oncology drugs aim to induce apoptosis. Unfortunately, p53, the master mediator of apoptosis and target for upregulation with such treatments, and its key cofactors are absent/nonfunctional in HCC.

This new discovery regarding *GATA4* indicates that we can use therapies to inhibit the enzymes that silence rather than activate genes (corepressors like DNA methyltransferases), so that the hepatocyte development process can be completed and produce epithelial cells that focus on specialized functions instead of replication. Our research team is testing new treatments that work this way in mice, including new versions of DNA methyltransferase-inhibiting drugs decitabine and 5-azacytidine that can distribute into the liver and into liver cancers. We are hoping to move to clinical trials in about a year.



CHAIRMAN'S Q&A

Brian J. Bolwell, MD, FACP, Addresses the Challenges of Leadership in Academic Medicine

Dr. Bolwell is Chairman of Taussig Cancer Institute.

He can be reached at bolwellb@ccf.org or 216.444.6922.

On Twitter: [@brianbolwellmd](https://twitter.com/brianbolwellmd)

In our last Q&A, you addressed using a serving leadership style to lead through change. Remind us what you mean by serving leadership and why you believe it's important.

Serving leadership is more of a viewpoint. It's a belief that the team is more important than the leader as an individual. And that core belief leads to what I think are the central tasks of a good leader. First, you have to set and communicate a clear vision. That is harder than it sounds, especially since that vision tends to evolve over time, as mine has for the Cancer Center.

Your next job is to be very involved in the process of recruitment. You want good people who understand or who are willing to understand the vision. Then, give them what they need to succeed, and remove barriers. Addressing challenges, which frequently are political, is a huge part of being a serving leader.

And if you do these things, your team will succeed. And that success needs recognition, and as a leader, you should be enabling but not participating in that recognition. It's not about you.

That's certainly the kind of leadership style I aspire to.

What's unique about leading an academic medical center?

Academic medicine rewards people who celebrate their own work. That's how you get grants; that's how you get promoted. Success is defined by individual accomplishment. But if you're a serving leader, success is defined by the team. Those are two very different things.

I think that often in academic medicine people who excel individually are elevated into leadership roles that require very different skills, skills that aren't practiced or rewarded in individual careers. Frequently, leaders in our field don't do as well as they otherwise could because they've historically been rewarded for individualistic work. And that in my mind is exactly the wrong thing to do as a leader of a big organization.

Leadership is not in any way, shape or form about your own personal success. I've frequently said that I don't think a leader should be first author on any paper once they have a leadership position, and I really believe that to be true. But that's very hard for a lot of people to do. But if you're going to lead successfully, you've got to let other people do that.

You've got to be OK recruiting really, really good people, even if it means that your own personal recognition will diminish.

How do you set a vision for an organization? You noted that it's more complicated than it sounds.

Well, it is. I think you have to walk the walk first. You've got to demonstrate to everyone what your own personal priorities are. Our focus is the delivery of great clinical care in a compassionate and empathetic way, and it's my job to keep that front and center. It's our single most important priority, and that's why we care so much about access.

You also need to build a culture around those priorities. One of the things we do is circulate patient stories to everyone who works in the Cancer Center, from the front desk staff to researchers. It reminds people that there is a gravity to what we do, a seriousness, and it's very important that our staff stay focused on the patient's perspective. For patients, their cancer journey is far and away the most important thing in their lives. This isn't like coming in to check up on a cold. This is life-changing. So I think one of the crucial aspects of leading a cancer center is to continually elevate a culture that centers empathy and excellence.

In our last interview you mentioned that you've read more than 40 books on the topic of leadership. What do you think those books miss that has been really important to your leadership style?

There are a few things, but one of the most important is courage. If you're going to be an effective leader, you've got to do the right thing.

I remember being on weekend service with a very challenging attending during my fellowship. We had a very sick patient, and we needed something done. Everyone else was more than willing to wait until Monday. But this attending went into his office and made innumerable calls to other attendings in the organization to make sure the patient got what they needed right away. He was really passionate about that, and that moment reinforced in me that it is important to advocate for your patients.

He had the courage to do what needed to be done, even if it bothered other leaders on a weekend. In addition to advocating for patients and for your staff, being able to do what needs to be done generates respect, loyalty and trust from the people you serve.

What's your best advice to existing or aspiring physician leaders?

Study the subject. I mean, if you're a leukemia doc, you had to study and know everything there is to know about leukemia. It's the same with leadership. Some people make the mistake of not studying leadership and just assuming they know everything. I made that mistake myself in the beginning.

But the more you can learn about a topic, the better you can get. You can teach an old dog new tricks as long as the old dog wants to learn; if you want to be a better leader, you can be if you work at it. That's my best advice.



Rarely Studied Gene Plays Role in **Predisposition** to **Thyroid Cancer**

A variant in the rarely studied gene *USF3* may predispose individuals to thyroid cancer.

Dr. Eng is Chair of the Genomic Medicine Institute, staff in the Department of Hematology and Medical Oncology and Professor of Molecular Medicine at Cleveland Clinic Lerner College of Medicine. She holds the Sondra J. and Stephen R. Hardis Endowed Chair of Cancer Genomic Medicine. She can be reached at engc@ccf.org or 216.444.3440. On Twitter: @CharisEngMDPhD

Differentiated thyroid cancer (DTC) is the fastest-rising incident cancer in the U.S. Although epidemiologic studies show that thyroid cancer is the most familial of all solid tumors, the known genes predisposing to DTC do not account for all of the familial nature of DTC.

Charis Eng, MD, PhD, is an expert in the study of Cowden syndrome (CS), an autosomal disorder that predisposes individuals to breast, thyroid and other epithelial cancers. With up to 50 percent of CS patients testing negative for all known genetic mutations, the syndrome remains an underdiagnosed and difficult-to-recognize condition.

Dr. Eng's team in the Genomic Medicine Institute discovered a novel genetic cause for CS/CS-like disorder by focusing on thyroid cancer predisposition in a family with CS and thyroid cancer, and published this discovery in *Human Molecular Genetics*. Using a combined family-based, whole-genome sequencing strategy, the team identified an inherited variant (a compound heterozygous deletion) in *USF3* in a subset of heritable CS/CS-like patients.

***USF3* deletion, malfunction enhances EMT signature**

The deletion or malfunction of *USF3* causes a very stressful microenvironment, including metabolic issues and structural instability of the cell. The metabolic issues stem from an enhanced epithelial-to-mesenchymal

transition (EMT) signature, which is known to cause tumor progression and metastasis. The cell surface is also compromised from necrosis-like features and impaired respiratory capacity, all of which are hallmarks of cancer.

Additionally, of the nine family members studied, seven were affected with papillary thyroid cancer. Dr. Eng's team found the *USF3* deletion in those family members affected with thyroid cancer and thus suspected that *USF3* may be involved in a predisposition toward thyroid cancer.

Potential treatments and preventive measures

The researchers also discovered a potential therapeutic strategy given *USF3*'s glutamine-dependent cell survival advantage. Like most tumor cells, *USF3*-deficient cells actually can survive low-glucose conditions, but this survival requires glutamine supplement, suggesting that glutamine removal might have therapeutic potential in patients with *USF3*-related thyroid cancer.

The discovery of this cancer-predisposing gene will facilitate predictive genetic testing, risk assessment, genetic counseling and clinical management of the disease. Currently there is no genetic test for *USF3*, but these findings could improve therapeutic and preventive interventions for both sporadic cancer and cancer predisposition in similar mechanisms.



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\$4.1 million



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Since 2014, VeloSano has raised more than \$12.4 million in the fight against cancer. VeloSano 5 weekend is scheduled for July 20-22, 2018. Register at velosano.org.

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Ahmad Tarhini, MD, PhD

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Dr. Tarhini joins us from the University of Pittsburgh Medical Center, where he was Associate Professor of Medicine in the Clinical and Translational Science Institute and the Division of Hematology-Oncology.



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