

## Expectations about New Cancer Treatments

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### Abstract

In 2015, Michael D. Becker, a former biotech executive, was diagnosed with head and neck cancer, which was caused by human papillomavirus (HPV), a sexually transmitted infection. Mr. Becker knows a lot about cancer and cancer drug development, used his expertise in the drug industry to consider possible treatment options. One he was enthusiastic about was the cancer immunotherapy. Unlike chemotherapy, which involves administering powerful drugs that kill both cancerous and healthy cells (most healthy cells can repair themselves), immunotherapy harnesses the power of the immune system to help it identify and knock out just the cancerous cells.

**Keywords:** Head and Neck Cancer, Chemotherapy, Immunotherapy, Human Papillomavirus, Checkpoint Inhibitor, the Median Survival Rate, Cure

### Introduction

Cancer treatments have generated a lot of buzz lately. In 2016, for instance, former President Jimmy Carter announced he was cancer-free using the immunotherapy Keytruda as part of his treatment for melanoma. There's been a surge of investment in cancer therapies in the past few years as well, with global spending on cancer treatments hitting \$113 billion in 2016 in the USA. Mr. Becker is currently being treated for his cancer, and considered using an approved cancer immunotherapy. There are a number of drugs that have been approved in the past few years for a wide array of cancers from melanoma, to lung cancer. It's led to a big marketing push to raise awareness for immunotherapy and new treatments. There was commercial information suggesting that, for example, lung cancer can be cured with growing chance. But when patients have looked at immunotherapy for his own cancer, reality set in.

### How Long Patients on the Treatment Tended to Survive

The majority of the patients who got a checkpoint inhibitor (called nivolumab), don't respond to the treatment or have much of under a benefit. The median survival rate (a measure of how long patients on the treatment tended to survive) was only a couple of months longer than chemotherapy, and even it was under a year. You may not be talking a long term survival or anything like that. At the end of the day it was only 20% that got sustained benefit or a cure.

Those odds weren't good enough to convince patients to try. Some of them opted instead to enroll in a trial that explores the effects of M7824, a drug that combines the same checkpoint inhibitor as nivolumab, but packed in an extra punch with another target. In the end, cancer has still progressed.

So even though there are some new immunotherapy treatments one expert called "the most exciting thing I've seen in my lifetime", there is still a long way to in making sure the majority of cancer patients respond to treatment. Patients tend to think cancer's just about to be cured, when they have a little bit more work to do. They can pop that bubble or at least reset to have dialed down expectations for some of these breakthroughs make that in the public's best interests [1].

### Hidden Direct Link Between Calcium and Cholesterol

Calcium is essential for strong bones and teeth, but new research shows it also plays a key role in moderating another important aspect of health: cholesterol. Researchers at the University of Alberta and McGill University have now discovered a direct link

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between calcium and cholesterol. This discovery could pave the way for new treating of high blood cholesterol.

The research began with studying the role of a calcium-binding protein. They noticed an extreme rise of blood cholesterol concentration in mice when the protein was not present. To follow up on this observation, Professor Marek Michalak with colleagues discovered the physiological link between calcium and cholesterol is also preserved in worms.

There is a mechanism inside the cell that senses when there is not enough cholesterol present and turns on the machinery to make more. What they found is that a lack of calcium can hide cholesterol from the machinery. If you lose calcium, your synthetic machinery thinks (!) there's no cholesterol and it starts making more even if there is already enough.

Factors that affect blood cholesterol concentration have been studied for a long time. The general belief was that cholesterol controlled its own synthesis inside of cells. Now, with above discovery that calcium can control that function too. Finding this link potentially opens a door to developing new ways of controlling cholesterol metabolism.

The researchers consider their finding a significant step toward developing different approaches to patient care in the future. They are now looking to discover the common factor that allows calcium and cholesterol to communicate with each other in the cell [2].

### Calcium-Binding Protein Inhibits Cholesterol Efflux

The ABC transporter ABCA1 has been implicated to control cholesterol efflux in a variety of cell types including macrophages, fibroblasts, and intestinal epithelial cells. Anionic peptide fraction/calcium-binding protein (APF/CBP) inhibited ApoA-I mediated cholesterol efflux from normal fibroblasts in a dose dependent manner but had no effect on specific efflux to methyl-beta cyclodextrin or phosphatidylcholine liposomes. In ABCA1 deficient fibroblasts no effect of APF/CBP on efflux was seen. We conclude that APF/CBP specifically interferes with ApoA-I mediated cholesterol trafficking. Probably the competitive binding to ABCA1 may explain the decreased ApoA-I mediated efflux from fibroblasts [3].

Cholesterol controls the activity of a wide range of membrane receptors through specific interactions and identifying cholesterol recognition motifs is therefore critical for understanding signaling receptor function. The membrane-spanning domains of the paradigm neurotransmitter receptor for acetylcholine (AChR) display a series of cholesterol consensus domains (CARC). The CARC-cholesterol interaction is of high affinity, lipid-specific, concentration-dependent, and sensitive to single-point mutations. The CARC motif is generally located in the outer membrane leaflet and its reverse sequence CRAC in the inner one. Their simultaneous presence within the same transmembrane domain obeys a "mirror code" controlling protein-cholesterol interactions in the outer and inner membrane leaflets.

Deciphering this code enabled us to elaborate guidelines for the detection of cholesterol-binding motifs in any membrane protein [4].

### Blood Test to Detect Brain Treatable Metastases

Houston Methodist cancer researchers are closer to creating a blood test that can identify breast cancer patients who are at increased risk for developing brain metastasis, and monitor disease progression and response to therapy in real time.

The discovery of identifying a distinct group of cells in the bloodstream of patients who have breast cancer brain metastases could lead to the creation of more sensitive screening tools. In the Aug. 4 online issue of Nature Communications, a proof-of-concept study led by Dario Marchetti, Ph.D., detected a distinct group of circulating tumor cells (CTCs) associated with brain metastasis. The finding brings cancer researchers closer to understanding how the seeds of metastatic disease can thrive in breast cancer patients and cause it to spread to the brain.

Their research confirmed that CTCs in breast cancer brain metastases are distinct from other circulating tumor cells. Unlocking the mystery of how these seeds of metastatic disease survive and thrive over a period of years, sometimes decades, is an enigma in cancer.

Magnetic resonance imaging is the accepted standard-of-care to diagnose breast cancer brain metastasis (BCBM) in patients. According to extensive clinical studies, approximately 20 percent of breast cancer patients will develop brain metastasis over their lifetime, in general, metastatic disease to the brain is estimated to become the number one cancer killer within the next decade.

It is a first comprehensive report of patient-derived circulating tumor cells at the gene expression level, so we now have a clear picture of the signaling pathways that allows them to establish brain metastases. By comparing the whole genome expression patterns of CTCs isolated from patient blood samples diagnosed with or without BCBM, they uncovered a 126 gene-signature that is specific to these brain metastatic CTCs, said Debasish Boral, Ph.D., the paper's first author and a research associate with the Biomarker Research Program at Houston Methodist Research Institute.

This research builds on a 2015 research paper of Marchetti's lab about four distinct circulating tumor cell subsets that were implicated in breast cancer cell dormancy. Viable breast cancer cells can remain dormant in the patient's bone marrow or other organs like the brain, lungs and liver, even decades after a primary tumor is surgically removed. These scattered cells are often undetectable by traditional clinical tools, making it nearly impossible to detect and treat metastatic disease while still amenable to therapy.

The Houston Methodist researchers are now focused on broadening the study patient population, with the end goal of transforming this information into development of two kinds of non-invasive liquid biopsies that could be used by treating physicians: a screening method to predict brain metastasis before the disease is detectable by current diagnostic standards (MRI), and other to monitor treatment efficacy in real-time in those patients diagnosed with brain metastasis [5].

### Senator John McCain returned after his Surgery

Eight years ago when the last national battle around health care was going, one senator paid tribute to another who had just

passed away: "I think we may have made progress on this health-care issue if he had been there. He had this unique capability to sit people down at a table together... and really negotiate, which means concessions." The senator was John McCain (R-Ariz.), and he was referring to Ted Kennedy. In a cruel twist, McCain now has the same form of brain tumor, glioblastoma (GBM), that afflicted Sen. Kennedy (D-Mass.).

GBM is a highly contingent disease. Survival depends on the size, location, genetic composition of the tumor, and a range of other factors related to the patient's overall level of health. No two GBM patients are identical. The statistics about survival rates include elderly and young people, those with tumors that are inoperable, and those with genetic mutations that will be more or less responsive to existing therapies. Still, there is no escaping the reality that long-term survival is rare.

If the doctors' reports are accurate, McCain starts at an advantage, having already undergone surgery, they told CNN. At the end of July 2017 he returned to Washington and delivered a rousing 15-minute speech on the floor of the Senate when many patients struggle with language months after undergoing similar procedures. (Kennedy's case was more complicated, and top national neurosurgeons were divided about whether to operate at all. His tumor was also located in a different part of the brain-another contingency.)

McCain, his family and his medical team are now reportedly considering his treatment options. The standard of care for GBM, as his doctors have explained, includes a combination of radiation and chemotherapy. The typical regimen includes six weeks of radiation, or 30 sessions. At the same time, patients take a low dose of an oral chemotherapy agent, temozolomide. This pill is usually tolerated more easily than intravenous chemo agents, though it, includes its own set of side effects.

There are two main obstacles to long-distance travel during this period: first, the cumulative effect of the radiation and chemo tends to cause fatigue. But beyond fatigue, plane travel will be a challenge. Chemo lowers the immune system's ability to fight off illness so blood counts have to be monitored closely. Four-hour plane rides in close quarters with other people and their bacteria and viruses are not exactly ideal for healing.

If he follows the standard of care, McCain will likely get a few weeks off after radiation, then will start a new chemo-only routine that involves taking a higher dose of the oral agent five consecutive days a month for six months depending on his response and the recommendations of his oncologist. It is also possible McCain's doctors will recommend a clinical trial, of which there are several for glioblastoma patients since the disease is an active research arena for scientists, especially in the burgeoning field of immunotherapy.

McCain is blessed with two things needed to endure cancer: a first-class medical team and a tight-knit support network. The third pillar is a sense of purpose. Depression and anxiety commonly accompany cancer diagnoses. A commitment to family or another mission can exponentially help minimize the tedium and physical toll of treatments.

McCain's personal health crisis has arrived at the peak of the congressional debate over health care. U. S. Vice President Pence had to cast the deciding vote in a divided Senate just to allow the

Republicans to introduce their various formulas for repealing the Affordable Care Act. Still, McCain voted with the Republican Party line to open debate. Now McCain can live true to his words. Without his vote, the repeal effort that will force millions off health care could fail. He told: "The times when I was involved even in a modest way with working out a bipartisan response to a national problem or threat are the proudest moments of my career, and by far the most satisfying."

McCain is undoubtedly a national hero. Now he can cement his legacy as a lawmaker by helping to depolitize the health-care debate and "sit people down at a table and really negotiate"- as he once said about Kennedy [6].

### Want to stay young?

Eat green and enjoy being young! A group of researchers from the University of Iowa found that eating green apples (unpeeled) and green tomatoes can help reduce muscle aging and muscle loss in elderly years.

According to the researchers, people who eat green apples and green tomatoes for at least 2 months may experience the benefits, which are attributed to the potent chemicals tomatine and ursolic acid that are present in and green tomatoes and green apple peel and respectively.

Gene alteration initiated by a protein ATF4 is accountable for muscle wastage in the older people, but researchers said that tomatine and ursolic acid may significantly decrease the activity of this protein, which in turn decreases muscle decay and aging. The chemicals could prevent muscle decay as they disable genes that the ATF4 usually activates.

According to the researcher Christopher Adams, an internal medicine professor, tomatine and ursolic acid appear to have a great potential as implements for dealing with atrophy and muscle weakness during aging.

Moreover, by decreasing ATF4 activity, tomatine and ursolic acid allows skeletal muscle to recuperate from effects of aging. Prof. Adams and other experts in the research hope that the results of the study will help determine the precise factors that cause aging in the people.

Green tomatoes contain tomatine, an alkaloid that can fight cancer cells. Tomato plants use their tomatine content to fight bacteria, viruses, insects, and fungi. The researchers found that green tomato extract can strongly inhibit cancer cell lines of the colon, breast, liver, and stomach. A green tomato is also a rich source of many essential vitamins, including Vitamin C, Vitamin A, Vitamin K, and B-Complex Vitamins, minerals, antioxidants, protein, and fiber.

These tomatoes can help prevent premature aging and protect the immune system. Vitamin C also helps the absorption of iron in the body, therefore, it's truly beneficial to eat green tomatoes in a combination with some source of iron, such as poultry, meat, spinach, fish, or supplement.

Green apples provide numerous beauty and health benefits, especially when compared to red ones. The most significant green apple benefit is its dietary fiber content that aids in the regulation of bowel movements and thus helps in the overall digestive process. Due to the high fiber content, these apples, in turn, offer

another incredible benefit – prevention of colon cancer. The high levels of fiber in the green apple can help to reduce the levels of cholesterol. Green apple can also prevent digestive tract problems and reduce liver problems. They can help prevent diarrhea, as well as gout and constipation.

If you're a person focused on your skin health and beauty, then green apples are the ideal food for you. They contain Vitamins A, B, C, and E. If you regularly eat green apples (unpeeled) they will help in the whitening of skin - and keep the skin fresh and glowing.

Green apples contain both polyphenol and flavonoid- all forms of antioxidants. These powerful antioxidants can prevent DNA damage and various forms of cancer. Green apples contain organic acids that can improve appetite. If you suffer from low appetite as a reason of intestinal peristalsis, you can help this by consuming green apples. These apples are also energy giver. They contain carbohydrates that are mostly good for people leading a hectic life or playing any type of sport [7].

## Conclusions

There are very few specific or targeted inhibitors that are used in the treatment of brain cancer. There's really a dire need for new therapies and new ideas. MIT biologists have discovered a fundamental mechanism that helps brain tumors called glioblastomas grow aggressively. After blocking this mechanism in mice, the researchers were able to halt tumor growth. The researcher also identified a genetic marker that could be used to predict which patients would most likely benefit from this type of treatment. Glioblastoma is usually treated with radiation and the chemotherapy drug temozolamide, which may extend patients' lifespan but in most cases do not offer a cure. The reason is that there are very specific or targeted inhibitors that are used in the treatment of brain cancer. Recently there's a big dire request for new therapies and new ideas in this field, says Michael Hemman, an associate professor of biology at MIT, a member of MIT's Koch Institute for Integrative Cancer Research.

Drugs that block a key protein involved in the newly discovered process already exist, and at least one is in clinical trials to treat cancer. However, most of these inhibitors do not cross the blood-brain barrier, which separates the brain from circulating blood and prevents large molecules from entering the brain. The MIT team hopes to develop drugs that can cross this barrier, possibly by packaging them into nanoparticles.

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The results clarify ATF4 as a critical mediator of age-linked atrophy and muscle weakness, according to the reports of the study published in the *Journal of Biological Chemistry* (Sept. 3, 2016). These outcomes identify tomatine and ursolic acid as potential agents or/and principal compounds for decreasing ATF4 activity, atrophy, weakness in aged skeletal muscle.

Even though, the benefits of the 2 potent chemicals have already been proven in mice, further research still needs to be done in people. However, many previous studies have proven that people who eat green apples and green tomatoes are healthier.

McCain is blessed with two things needed to endure cancer: a first-class medical team and a tight-knit support network. The third pillar is a sense of purpose. Depression and anxiety commonly accompany cancer diagnoses. A commitment to family or another mission can exponentially help minimize the tedium and physical toll of treatments. A lifelong public servant has his mission at the ready.

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## Conflict of Interests

Author declares no conflict of interests.

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