Journal of Cancer Treatment and Research
2026, Vol. 14, No. 1, pp. 43–52
https://doi.org/10.11648/j.jctr.20261401.14

SciencePG
Science Publishing Group

Commentary

The Cancer Cocktail a Possible Treatment for Some Cancers

John Claras*

Independent Researcher, Sunnyvale Ca, United States

Abstract

Many cancers are glucose-dependent and have a higher rate of glycolysis, as described by the Warburg effect. Reducing the amount of free glucose will starve cancers. Medications that control blood glucose levels, including Metformin, change the intestinal biome by increasing desirable commensal bacteria, causing a drop in A1C. With the drop in glucose, many cancers can modulate metabolism to lipids, so a low-carbohydrate diet will keep the cancer from growing. Cancer can mask the immune system, turning off PD-L1 (Programmed Death Ligand^{-1}) and increasing the expression of CD47, the “do not eat me protein". CD47, a protein overexpressed on many cancer cells to prevent macrophages attacks. CD47 does this by binding to Signal Regulatory Protein Alpha (SIRPα) on macrophages. 4-Methylumbelliferone (4-MU) will limit the amount of masked CD47. 4-MU also has other benefits. It will protect the integrity of the B cells but also promotes insulin secretion to help cope with the degradation of B-cell function due to immune destruction. This might offset the side effects of Pembrolizumab (Keytruda), a therapeutic monoclonal antibody which targets and activates PD-1 on immune cells. PD-1 is a molecule that is found on killer T Cells and natural killer cells, which target any cell that does not display the MHC-2 cell surface molecule. These two changes, PD-L1 activation and CD-47 limitation, make cancer visible and vulnerable to Natural Killer cells, Killer T Cells, and macrophages. Pembrolizumab (Keytruda) can have toxic side effects, including a spike in blood sugar, which can damage B Cells, type 1 diabetes, and pancreatitis, though these are considered rare side effects. In Theory, Metformin and 4-MU will inhibit this occurrence with an improvement in gut bacteria and increasing insulin, and therefore lowering the risk to the pancreas and protecting B cells.

Keywords

Cancer, Cancer Pragmatic Switch, Cancer Adipose Tissue, Cancer Adipose Tissue Bloom, Adipose Tissue and Cancer Tumorigenesis, Cancer Stem Cell and Adipose Tissue

1. Introduction

The concept of cancer representing a pragmatic switch to eliminate excess glucose was first proposed in the paper “Cancer- the Pragmatic Switch to Combat Metabolic Syndrome” [1]. This work proposed the concept of cancer being a bidirectional switch that the body can use to combat metabolic syndrome. The hallmarks of many cancers includes a drastic increase in glucose consumption without using toxic oxygen and producing nontoxic lactate (glycolysis), metastases, and the

*Correspondence: John Claras (jclaras@onlinecables.com)

Received: 18 February 2026; **Accepted:** 9 March 2026; **Published:** 30 March 2026

ability to mask the cancer from the immune system by utilizing CD47 and PD-L1 proteins. The paper "Does Cancer Have a Benefit? - Your Immune System Might Think So" [5] showed that cancer-causing genomic changes have been in the genome for 240 million years, and if cancer has no benefit, the question arises why does it still exist. The immune system can easily kill cancer. Cancer must have a purpose; otherwise, it would have been deselected [5]. The paper "Is cancer the overflow of the adipose tissue" [12] shows how Cancer the Pragmatic Switch is under the control of the adipose tissue. The adipose tissue and cancer both have many common aspects: angiogenesis, regulation of CD47 and PD-L1, which affect the macrophages and natural killer cells. When the adipose tissue is overwhelmed for an extended period, it can call upon "Cancer the Pragmatic Switch to Combat Metabolic Syndrome," which converts large quantities of glucose into lactate before the organs are damaged. It is hypothesized that cancer arises from a stem cell that is turned on when adipose tissue is overwhelmed, suggesting that adipocytes support tumorigenesis. Adipose tissue and cancer have many similar qualities: ignored by the immune system, the ability to encourage angiogenesis [12], and both cancer and white adipose tissue undergo apoptosis in a low-glucose environment [45, 46]. Undiagnosed prostate, breast, and thyroid cancers are found next to adipose tissue in autopsies of people who died from something else. A primary tumor often secretes tumor suppressors to interfere with secondary tumor and metastases growth, and cancer, for the most part, is not contagious. We humans were designed to live in a calorie-scarce environment; before industrialized food supplies existed, the cycle of life included frequent starvation, which would cause adipose tissue and cancer to undergo apoptosis and disappear in the wild [1, 5].

2. CD44 and Cancer Stem Cells

The CD44 is a cell surface glycoprotein involved in various cellular processes such as cell adhesion, migration, and proliferation. Weng et al. [39] provided evidence that CD44 plays a key role in regulating adipocyte function, stating "that CD44 may be important in regulating adipose function through its direct action in adipocytes or adipocyte precursor" [39]. CD44 is also key to cancer progression from stem cells to metastases [35, 39]. In the paper "Is Cancer the Overflow of the Adipose Tissue?" [12], the theory is proposed that cancer and the adipose tissue are interrelated, and since cancer grows next to the white adipose tissue and uses it for fuel, the adipose tissue is controlling the development of cancer stem cells. CD44 signaling controls cancer stem cell development; CD44 promotes cancer growth, invasion, and metastasis by interacting with molecules like hyaluronic acid (HA). It is hypothesized in this paper that CD44 signaling needs to be shut down to combat cancer growth. Therefore 4-MU is needed to control hyaluronic acid and limit the expression of CD-44. Hyaluronic acid enhances cell adhesion and promotes cell migration, which is part of cancer metastasis [35]. The primary tumor is often not the problem; it is the metastasis and out-of-control development of cancer that leads to cancer lethality [39].

3. Treatment Protocol

A low-carbohydrate diet should be started immediately. Following the diet, Metformin has the lowest risk of the three treatments proposed and should also be started. Metformin will lower A1C and improve the gut biome. A1C reduction and improvements in the gut biome can lead to weight reduction and cause apoptosis of the white adipose tissue, and turning off "Cancer the Pragmatic Switch". If cancer growth is not stabilizing or reduced, then treatment with 4-Methylumbelliferone commences to deactivate the CD47 "do not eat me" protein to allow macrophage to see and attack the cancer cells. The side effects are minimal. If cancer still continues to grow, then treatment with Pembrolizumab will deactivate the PD-L1 protein, thus releasing natural killer cells to target and attack cancer cells. Natural killer cells will kill any cell not displaying the MHC-2 molecule. However, Pembrolizumab has serious side effects, as described below.

3.1. The Benefits of Metformin

Metformin (Metformin dimethylbiguanide hydrochloride), a commonly prescribed drug for type 2 diabetes, can significantly alter the composition of the gut microbiome by increasing biodiversity. Metformin's therapeutic effects include improved insulin sensitivity and glucose control, resulting in lower A1C, triglycerides, and lipids. Metformin can increase the abundance of specific bacterial groups, such as Akkermansia muciniphila, Escherichia coli, and A. muciniphila, which is particularly notable for its role in maintaining gut health and improving glucose metabolism. Conversely, metformin can reduce the abundance of other bacteria, such as intestinibacter bartletti. Metformin can promote the growth of bacteria that produce short-chain fatty acids like butyrate and propionate, which are beneficial for gut health and overall metabolism. The above, along with a healthy diet, will help turn off "Cancer the Pragmatic Switch" by altering the gut microbiome and lowering A1C and triglycerides by as much as 30%. Metformin can indirectly improve insulin sensitivity, which is crucial for managing type 2 diabetes [8, 9].

3.1.1. Side Effects of Metformin

Lactic Acidosis: This is a rare but serious side effect of metformin that can occur when the kidneys are not functioning correctly. Lactic acidosis can lead to fatigue, nausea, vomiting, and even death [37].

3.1.2. 4-Methylumbelliferone (4-MU) (Hymecromone) Benefits

4-MU has been in use for decades to treat biliary spasms (pain caused by bile duct contractions) and has been approved

for this purpose in Europe and Asia for over five decades. Hymecromone is typically administered orally. and is considered a safe and low-cost medication with few side effects. 4-MU primarily works by inhibiting the synthesis of hyaluronan (HA), a glycosaminoglycan found in connective tissues. This inhibition occurs by depleting the cellular pool of UDP-glucuronic acid, a precursor for HA synthesis, and by downregulating the expression of hyaluronan synthases. Hyaluronan is critical for the pathogenesis of diabetes [7]. Hyaluronic acid is the primary ligand for CD44 [20]. CD44 is a cell surface molecule with diverse roles in cancer, acting as both a tumor marker and a regulator of cancer progression and metastasis. It is often overexpressed in cancer cells, particularly cancer stem cells, and is involved in cell adhesion, migration, and invasion [35, 39]. 4-MU is quickly metabolized, which may affect its bioavailability, and can cause side effects such as gastrointestinal discomfort, allergic reactions, and, in rare cases, liver enzyme abnormalities. In addition, 4-MU can disrupt the CD47/SIRPα axis by disturbing glioblastoma and HA synthesis [35]. CD47 is overexpressed in cancer cells, which allows cancer cells to avoid detection and destruction by the immune system, particularly the macrophages [10, 16]. “Collectively, these findings indicated that HA plays a crucial role in macrophage polarization and CD47/SIRPα signaling between glioblastoma cells and macrophages” [13].

3.1.3. Side Effects

1) Significant downregulation of hyaluronan (HA) and chondroitin sulfate proteoglycans (CSPGs) throughout the body.
2) Increased bile acids in blood samples (reversible after wash-out).
3) Decrease blood sugars and proteins (reversible after wash-out).
4) Increased interleukins (IL10, IL12p70, IFN gamma) (reversible after wash-out).
5) Glycosuria (abnormal amount of glucose in urine) (reversible after wash-out).
6) Proteinuria (abnormal amount of protein in urine).
7) Significant increase in proerythroblasts in bone marrow (reversible after wash-out).
8) Mild reduction in forelimb grip strength (reversible after wash-out) [38].

3.2. Pembrolizumab (Keytruda ™)

Pembrolizumab (Keytruda) blocks interactions of the PD-1 protein expressed on the surface of immune cells with PD-L1 expressed on cancer cells. Interfering with PD-1 / PD-L1 interactions allows those immune cells (specifically T cells) to recognize and attack cancer cells. Essentially, it removes a "cloak" that some cancer cells use to hide from the immune system, allowing the body's natural defenses to target and destroy them. The immune system can identify and destroy cancer cells; however, expressing proteins like PD-L1 and PD-1 hides them from the natural killer cells and the killer T cells. PD-1 is a protein on the surface of T cells that acts as a "checkpoint." When PD-1 binds to PD-L1 on a cancer cell, it tells the T cell to stop attacking. This is a natural mechanism to prevent the immune system from attacking healthy cells. Pembrolizumab is a monoclonal antibody that binds to PD-1 on T cells. By blocking PD-1, Pembrolizumab prevents it from interacting with PD-L1 on cancer cells. This allows the natural killer cells and the killer T cells to become activated and attack the cancer cells. While Pembrolizumab can be very effective, it may not work for all patients or all types of cancer. The effectiveness can vary depending on the specific cancer type, the patient's individual characteristics, and whether the cancer cells express PD-L1 [17].

3.2.1. Side Effects

Because Pembrolizumab works by activating the immune system, it can sometimes cause the immune system to attack healthy organs and tissues, which range from mild to severe. Diagnosis involves blood tests to check for elevated blood sugar levels, autoantibodies (like anti-GAD65), and low C-peptide levels (which indicate reduced insulin production). Treatment typically involves insulin therapy to manage blood sugar levels, and in some cases, corticosteroids may be used to suppress the immune system. Due to the potential for severe complications, close monitoring of blood glucose levels and early recognition of symptoms are crucial for patients receiving pembrolizumab, particularly those with a history of autoimmune conditions or those who have also received other immune checkpoint inhibitors like ipilimumab [17].

3.2.2. Type 1 Diabetes Is Not Reversible

In most cases, type 1 diabetes induced by pembrolizumab is not irreversible, even after the drug is stopped. It is hoped that the addition of 4-MU and metformin will lower the blood sugar and protect the B Cells. This is an actively researched topic, but some studies indicate that low carb diets and pharmaceutical reduction of blood glucose loads can interfere with inflammation and reduce autoimmune-associated tissue defects- [22, 28, 44]. In theory, treatment with 4-MU and Metformin, plus a low-carbohydrate diet, should be able to counter the adverse effects of Pembrolizumab [17]. 4-MU has been shown to protect pancreatic beta cells by reducing hyaluronan, which otherwise promotes inflammation and autoimmune destruction. The combination of Metformin and 4-MU in theory should work together to lower the risks of Pembrolizumab. [18, 19].

3.3. A Low-Carbohydrate, Plant-based Diet Low in Lectins

It has been well documented that plant-based foods are generally considered very healthy due to their high nutrient density, fiber content, and potential to reduce the risk of various

diseases. They are rich in vitamins, minerals, antioxidants, and phytonutrients, which are all beneficial for overall health and well-being [11]. Protein should be very clean organic meats and fish, with an emphasis on cold water fish and essential oils such as oils high in polyphenols. See Doctor Li's excellent book "Eat to Beat Disease" [36]. The purpose of the diet is long-term remission of the "Cancer the Pragmatic Switch".

3.4. Prostate Cancer

Prostate cancer is a common cancer that starts in the prostate gland, which produces semen. In mice, prostate tumors were treated with 4-MU treatment, without serum/organ toxicity or weight loss; no tumors developed at one year, even after stopping the treatment at 28 weeks. 4-MU limits CD47 expression, leading to activation of macrophages. In addition, 4-MU had a potent antimetastatic effect, and might delay the progression to bone cancer [18]. CD44 was not correlated with the malignant state of prostate cancer. 4-MU inhibits HA synthesis, which plays a role in prostate cancer development, growth, and metastasis [18]. Men show that higher A1C levels are linked to more aggressive prostate cancer at the time of radical prostatectomy, including higher pathological Gleason scores. This association indicates that men with poorly controlled diabetes may have more aggressive tumors [30]. Metformin will reduce A1C along with a low-calorie, low glycemic index diet. 4-MU will activate macrophages. Pembrolizumab is as of now not a good option, since clinical trials by Merck were not successful for prostate cancer [43].

3.5. Breast Cancer

Breast Cancer is both common and deadly. Breast cancer cells can metastasize to other parts of the body, such as bones, liver, lungs, and brain. 4-MU abrogated CD44 signaling and prevented skeletal metastasis [14, 27]. These cancers express several CD44 isoforms, the most common being CD44v6. Treatment with Metformin and 4-MU, which suppresses CD44, reduced A1C and improved the intestinal biome [44]. Pembrolizumab blocks PD-L1 interaction with PD-1 on T cells and activates natural killer cells and killer T cells. Pembrolizumab is an effective immunotherapy drug for treating triple-negative breast cancer. This cancer lacks three key receptors: Estrogen receptor (ER), Progesterone receptor (PR), and Human epidermal growth factor receptor 2 (HER2). Treatment with Metformin for improving the intestinal biome and lowering A1C, along with a low-carbohydrate diet, is needed to make long term remission possible. Then, 4-MU is used to limit CD-47 expression and prevent metastasis. 4-MU inhibits hyaluronic acid (HA) synthesis, which is associated with the CD44. In addition, Pembrolizumab blocks PD-L1 interaction with PD-1 on T cells and thus leads to activation of natural killer cells and killer T cells.

3.6. Pancreatic Cancer

Pancreatic cancer forms when cells in the pancreas, often exocrine cells, grow uncontrollably and become malignant. Pancreatic ductal adenocarcinoma is the most malignant of all solid cancers because of the difficulties in early diagnosis and the poor response to chemotherapy. This cancer expresses several CD44 isoforms. 4-MU demonstrated antitumor effects in preclinical studies of pancreatic cancer, including inhibiting cancer cell proliferation and migration, and suppressing the accumulation of hyaluronan. Nagase et al. [21] first determined that 4-MU suppressed cell proliferation and invasion and increased apoptosis by inhibiting HA production. Nakazawa et al. showed that 4-MU inhibited HA synthesis and the formation of the pericellular HA coat in KP1-NL pancreatic cells and decreased liver metastases *in vitro* [24, 25]. Treatment with Metformin plus 4-MU (to suppress CD44) reduced A1C and improved the intestinal biome. The most consistent finding was that high A1C levels (≥10%) are linked to inferior overall survival, and A1C levels <5.0 to better outcomes [28]. In pancreatic cancer patients, Pembrolizumab will stop PD-L1-mediated inactivation of natural killer cells and killer T cells. Pancreatic cancer expresses several CD44 isoforms. Elevated CD44v3 levels can enhance the proliferation, migration, invasion, and stem cell-like properties of pancreatic cancer cells [26]. The low-carbohydrate diet will improve the intestinal biome and lower the A1C and assist in turning off "Cancer the Pragmatic Switch," making long-term remission possible.

3.7. Liver Cancer

Hepatocellular carcinoma, the most common type of liver cancer, originates in hepatocytes, the liver cells. Cholangiocarcinoma, on the other hand, is a cancer of the bile ducts, the tubes that carry bile from the liver to the gallbladder and small intestine. 4-MU is a potential treatment for hepatocellular carcinoma because it can inhibit cancer cell growth and induce cell death by macrophages, which are normally blinded by the cancer's overexpression of CD47. Its anti-tumor effects are linked to its ability to inhibit the synthesis of HA, a component of the extracellular matrix that is overproduced in liver cancer [31]. As with most cancers, higher A1C means lower survival: a study found the 3-year cumulative survival rate was significantly lower for patients with an A1C>7. Metformin will lower A1C with a goal of below 5.0. A low-carbohydrate diet will maintain a low A1C and assist in turning off "Cancer, the Pragmatic Switch", with a final goal of remission. Pembrolizumab blocks PD-L1 interaction with PD-1 on T cells and activates natural killer cells to target liver cancer cells effectively [8, 13].

3.8. Colorectal Cancer

Colorectal cancer is a cancer of the colon or rectum, which are parts of the large intestine. Most colorectal cancers start as

non-cancerous polyps that can gradually turn into cancer. Colorectal cancer, which is one of the most observed types of tumors worldwide, presents treatment limitations due to the necessity of surgical interventions and the high rates of metastasis and mortality. Again, high A1C is associated with poorer outcomes. The low-carbohydrate diet is essential, followed by Metformin, to further lower the A1C. 4-MU will lower A1C and also limit the cancer's ability to blind the macrophages using the CD-47 molecule. Heffler et al. showed that the inhibition of the hyaluronan HA decreases tumor growth and increases apoptosis [24]. While Pembrolizumab is approved for colorectal cancer, it is not a treatment option for all colorectal cancers. It is utilized specifically for MSI-H/dMMR tumors which are unresectable or show metastatic microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) [17]. A high A1C level is associated with a worse prognosis and lower survival rates for colorectal cancer. While some studies show no significant association between high A1C and overall survival, others highlight a negative impact, with some studies noting that a high A1C level is significantly linked to advanced stage and lower progression-free survival [32].

3.9. Melanoma

Melanoma cancers express several CD44 isoforms, the most common being the CD44v6. Studies indicate a complex relationship between melanoma and A1C. 4-MU lowers hyaluronic acid synthesis and prevent metastasis, and activate macrophages by lowering CD47 and inhibiting CD44. Pembrolizumab is an effective treatment for melanoma across various stages, including advanced, unresectable, and high-risk early-stage melanoma. It is approved as both an adjuvant therapy to prevent recurrence in patients with resected high-risk melanoma and as a treatment for advanced melanoma. Pembrolizumab blocks PD-1 interaction with PD-L1 on T cells and thus activates natural killer cells and killer T cells. Treatment increased survival in advanced melanoma, with 10-year follow-up data from KEYNOTE-006 demonstrating a 34% overall survival rate, compared to 23.6% with Ipilimumab, another anti-cancer immunotherapy drug. One study shows improved clinical outcomes in diabetic melanoma patients exposed to metformin [29]. The low-carbohydrate diet will help lower A1C alone, the addition of Metformin should limit the side effects of pembrolizumab and to improve the outcomes and help to shut down “Cancer the Pragmatic Switch”.

3.10. Glioblastoma

The low-carbohydrate diet is critical for Glioblastoma, along with Metformin. High A1C levels are associated with shorter survival for glioblastoma patients. 4-MU is a small molecule and can cross the blood-brain barrier with the hope of limiting the CD47, which blinds the macrophages to the presence of cancer cells. Also, 4-MU will reduce the amount of hyaluronan, thus limiting CD44 signaling [14]. Type 2 diabetes, as well as obesity, have been identified as independent risk factors of poor prognosis in patients with high-grade gliomas [15]. Pembrolizumab has demonstrated significant efficacy in recurrent glioblastoma patients with high tumor mutation burden and mismatch repair deficiency (dMMR) [2]. Pembrolizumab blocks PD-L1 interaction with PD-1 on T cells [4], which activates natural killer cell and killer T cells. Research shows that 4-MU can reduce Glioblastoma cell proliferation, migration, and survival in vitro and in animal models. It has also demonstrated the ability to sensitize GBM cells. 4-MU will lower the hyaluronic acid synthesis and prevent metastasis, and activate macrophages by lowering CD47 and inhibiting CD44. Pembrolizumab does not readily cross the blood-brain barrier (BBB) to treat glioblastoma effectively [40].

3.11. Ovarian Cancer

Ovarian cancer is one of the most frequent gynecological pathologies in adult women. It has a high mortality rate since it metastasizes early and quickly, presenting high resistance to chemotherapy in women with high A1C levels. The low-carbohydrate diet is critical, along with Metformin, to lower the A1C and improve the intestinal biome. It was found that 4-MU inhibited ovarian cancer cell proliferation in a dose-dependent manner *in vitro*, but also found non-inhibitory effects of 4-MU on cell invasion and migration [23]. Furthermore, 4-MU limits the amount of hyaluronic acid synthesis and prevent metastasis, and activate the macrophages by lowering levels of CD47 and inhibiting CD44. It is hoped that both metformin, 4-MU and a low carbohydrate diet will turn off “cancer the pragmatic switch”. Pembrolizumab is approved for the treatment of primary advanced or recurrent endometrial carcinoma, and as a single agent in microsatellite instability-high or mismatch repair-deficient endometrial carcinoma that is not eligible for curative surgery or radiation [33, 34]. Pembrolizumab blocks PD-L1 interaction with PD-1 on T cells, leading to activation of natural killer cell and killer T cells. It is hoped that with a low carbohydrate diet that remission is possible.

3.12. Lung Cancer

Lung Cancers two major groups are Non-Small Cell Lung Cancer which is the most common at 80-85% of lung cancer, includes adenocarcinoma and squamous cell carcinoma. The 2nd type is Small Cell Lung Cancer which is more aggressive, starts in hormone-producing cells, and often spreads quickly [47]. 4-Methylumbelliferone (4-MU) shows significant promise in lung cancer research as a metabolic modulator that enhances immunotherapy, particularly anti-PD-1, by targeting the tumor's acidic, immunosuppressive environment, inhibiting cancer stem cells, reducing tumor growth, and improving immune cell infiltration. By normalizing the TME, 4-MU makes tumors more susceptible to immune attack, boosting

the effectiveness of checkpoint inhibitors like Pembrolizumab. In vitro, 4-Mu reduced CAIX expression, shifted macrophage polarization toward a pro-inflammatory phenotype, and enhanced CD8+ T cell infiltration. 4-Mu was safe and well tolerated, and notably, combined with anti-PD-1 therapy, it synergistically inhibited tumor growth and increased both CD4+ and CD8+ T cell infiltration [41]. Pembrolizumab is effective for various stages and types of lung cancer, including non-small cell lung cancer (NSCLC), significantly improving survival and reducing disease progression when used alone or with chemotherapy, and even helping prevent recurrence after surgery. Pembrolizumab blocks PD-L1 interaction with PD-1 on T cells, leading to activation of natural killer cell and killer T cells. It is hoped that with a low carbohydrate diet that remission is possible [42]. Elevated A1C levels (typically ≥7.0%) at diagnosis or before treatment are linked to shorter overall survival. Conversely, patients with optimal glycemic control (A1C <6.5%) often show improved survival rates [48].

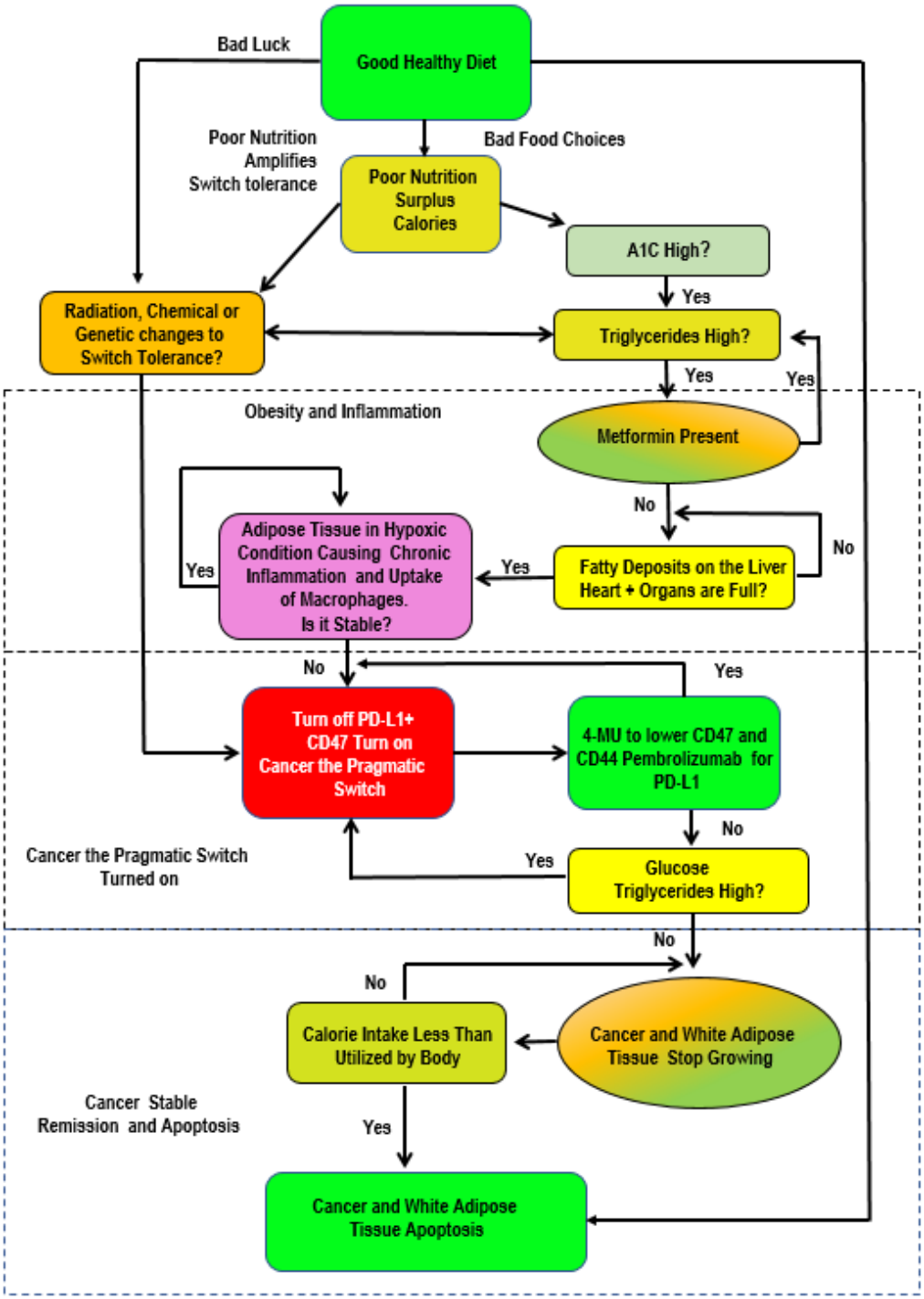

Figure 1. *Cocktail Flow Chart.*

4. Discussion Integrating Mainstream Oncology with Cancer the Pragmatic Switch

To integrate "Cancer the Pragmatic Switch" to "Mainstream Oncology" the theory has been presented at several forums over the last few years. The following proposed treatments are putting together documented Oncology methods to produce a "Systems Biology" Approach to Cancer using "Cancer the Pragmatic Switch" model [1]. The below cancers are categorized with an integrated approach. It is well established that the CD-47 "Don't Eat Me" molecule turns off the Macrophage. 4-MU is used to counter this [6]. Cancer turns off the PD-L1 which quiets the Natural Killer Cell and the Killer T-Cell. To counter this Pembrolizumab is used as a check point inhibitor. Pembrolizumab can damage the Beta cells with rapid spike in blood sugar and A1C, it is a rare side effect occurring in roughly 0.1% to 2% of patients [42, 43]. To counter this Metformin is used which is excellent at controlling A1C. Metformin and 4-MU have the potential to offset the risks to Pembrolizumab. As stated above 4-MU has been shown to protect pancreatic beta cells by reducing hyaluronan synthesis, which otherwise promotes inflammation and autoimmune destruction [3]. This combination of Metformin and 4-MU should in theory work together to lower the risks of Pembrolizumab [13]. It is well documented that Metformin and 4-MU lowers A1C. It is well documented that a lower A1C increases cancer survival. As stated above 4-MU limits the hyaluronan synthesis which is a key component in CD-44 expression causing Metastasis [7]. Finally, it is well documented that diet improves survivability which is part of the Cancer the Pragmatic Switch Model [1]. The systems approach uses the Pragmatic Switch model to reverse key components of cancer.

5 Conclusion

In the paper "Cancer: The Pragmatic Switch" [1] a concept was delineated that proposed that cancer functions like a switch that is turned on with too much glucose, lipids, and fats in the diet. Cancers use CD47 to mask the macrophages from the immune system, and PD-L1 neutralizes the natural killer cell, blinding its ability to kill Cancer. In the paper "Is Cancer the Overflow of the Adipose Tissue?" [12] the white adipose tissue is hypothesized to controlling the cancer stem cell and the upregulation of the CD47 "Do not Eat me" and the PD-L1 "Do not see me" cell surface proteins. 4-MU inhibits hyaluronic acid synthesis, making CD44-role in metastasis limited. The paper "Does Cancer Have a Benefit - your immune system might think so" [5] it is proposed that cancer's purpose is to rid the body of excess glucose, fats, and lipids, and this mechanism has been around for 240 million years with exactly that purpose. There needs to be a multi-stage approach to putting cancer in remission: [A] Low-carbohydrate diet rich in proper nutrition to improve the intestinal biome and reduce glucose, triglycerides, and lipids. [B] Metformin to improve the intestinal biome and lower the A1C. High A1C levels have poorer outcomes for all cancers. [C] 4 Methylumbelliferone (4-MU) to lower the hyaluronic acid synthesis and prevent metastasis, and activate the macrophages by lowering CD47 levels and inhibiting CD44. [D] Lastly, Pembrolizumab blocks PD-L1 interaction with PD-1 on T cells, which activates natural killer cells and killer T cells. One significant side effect of Pembrolizumab is irreversible type 1 diabetes. It is hoped that with a low-carbohydrate diet plus both Metformin and 4-MU, this will occur less frequently. These drug interrelationships need to be studied to determine efficacy plus safety and formulate the proper dose based on sex, weight, and progression of cancer. It is hoped that Metformin and a low-carbohydrate diet will put the cancer into remission and turn off "Cancer the Pragmatic Switch" The other drugs proposed will shrink tumors and rid the body of cancer.

Abbreviations

4-MU	4-Methylumbelliferone
A1C	A Measure of Blood Sugar (or HbA1c)
PD-1	Programmed Death-1- Immune Checkpoint for the T-Cell
PD-L1	Programmed Death Ligand 1- Found on the Surface of cells
CD-44	Receptor For Hyaluronic Acid
CD-47	Prevent the Macrophages from Destroying the Cell

Author Contributions

John Claras: Conceptualization, Format analysis, Funding acquisition, Investigation, Methodology, Project Administration

Conflicts of Interest

The author declares no conflicts of interest.

References

[1] Claras, J Cancer—A Pragmatic Switch to Combat Metabolic Syndrome? Oncol Rev., 15 February 2023. https://doi.org/10.3389/or.2023.10573

[2] Pibuel, M. A., Poodts, D., Sias, S. A. *et al.* 4-Methylumbelliferone enhances the effects of chemotherapy on both temozolomide-sensitive and resistant glioblastoma cells. *Sci Rep* 13, 9356 (2023). https://doi.org/10.1038/s41598-023-35045-3

[3] Zhang, W.; Yang, S.; Yu, X.; Zhu, S.; Wang, X.; Sun, F.; Liang, S.; Wang, X.; Zhao, G.; Gao, B. Beneficial Actions of 4-Methylumbelliferone in Type 1 Diabetes by Promoting β Cell Renewal and Inhibiting Dedifferentiation. *Biomedicines* 2024, *12*, 2790. https://doi.org/10.3390/biomedicines12122790

[4] Dzienis M, Cundom J, Fuentes CS, Spreafico A, Nordlinger M, Pastor AV, Alesi E, Neki A, Fung AS, Figueiredo Lima IP, Oppelt P, da Cunha Junior GF, Burtness B, Franke FA, Tseng JE, Joshi A, McCarthy J, Swaby R, Sidi Y, Gumuscu B, Naicker N, de Castro G Jr. Pembrolizumab Plus Carboplatin and Paclitaxel as First-Line Therapy for Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (KEYNOTE-B10): A Single-Arm Phase IV Trial. J Clin Oncol. 2024 Sep 1; 42(25): 2989-2999. https://doi.org/10.1200/JCO.23.02625

[5] John Claras. (2023). Does Cancer Have a Benefit? - Your Immune System Might Think So. Biomed J Sci & Tech Res 53(3). BJSTR. MS. ID.008406.

[6] Pibuel MA, Díaz M, Molinari Y, Poodts D, Silvestroff L, Lompardía SL, Franco P, Hajos SE. 4-Methylumbelliferone as a potent and selective antitumor drug on a glioblastoma model. Glycobiology. 2021 Jan 9; 31(1): 29-43. https://doi.org/10.1093/glycob/cwaa046

[7] Nagy N, Kaber G, Johnson PY, Gebe JA, Preisinger A, Falk BA, Sunkari VG, Gooden MD, Vernon RB, Bogdani M, Kuipers HF, Day AJ, Campbell DJ, Wight TN, Bollyky PL. Inhibition of hyaluronan synthesis restores immune tolerance during autoimmune insulitis. J Clin Invest. 2015 Oct 1; 125(10): 3928-40. https://doi.org/10.1172/JCI79271

[8] Gong Z, Aragaki AK, Chlebowski RT, Manson JE, Rohan TE, Chen C, Vitolins MZ, Tinker LF, LeBlanc ES, Kuller LH, Hou L, LaMonte MJ, Luo J, Wactawski-Wende J. Diabetes, metformin and incidence of and death from invasive cancer in postmenopausal women: Results from the women's health initiative. Int J Cancer. 2016 Apr 15; 138(8): 1915-27. https://doi.org/10.1002/ijc.29944

[9] Rosell-Díaz, Marisel, et all Metformin-induced changes in the gut microbiome and plasma metabolome are associated with cognition in men Metabolism VL 157 155941 2024 2024/08/01/ 0026-0495 https://doi.org/10.1016/j.metabol.2024.155941

[10] Vitale Daiana L., Icardi Antonella, Rosales Paolo, Spinelli Fiorella M., Sevic Ina, Alaniz Laura D. Targeting the Tumor Extracellular Matrix by the Natural Molecule 4-Methylumbelliferone: A Complementary and Alternative Cancer Therapeutic Strategy Frontiers in Oncology, Volume 11 - 2021 2021. https://doi.org/10.3389/fonc.2021.710061

[11] Jenkins DJA, Wong JMW, Kendall CWC, et al. The Effect of a Plant-Based Low-Carbohydrate ("Eco-Atkins") Diet on Body Weight and Blood Lipid Concentrations in Hyperlipidemic Subjects. *Arch Intern Med.* 2009; 169(11): 1046-1054. https://doi.org/10.1001/archinternmed.2009.115

[12] John Claras, (2024), Is Cancer the Overflow of the Adipose Tissue? Clinical Reviews and Case Reports, 3(6); https://doi.org/10.31579/2834-5061/008

[13] Yan, T., Wang, K., Li, J. *et al.* Suppression of the hyaluronic acid pathway induces M1 macrophages polarization via STAT1 in glioblastoma. *Cell Death Discov.* 8, 193 (2022). https://doi.org/10.1038/s41420-022-00973-y

[14] Chen, C., Zhao, S., Karnad, A. *et al.* The biology and role of CD44 in cancer progression: therapeutic implications. *J Hematol Oncol* 11, 64 (2018). https://doi.org/10.1186/s13045-018-0605-5

[15] Mazurek M, Litak J, Kamieniak P, Kulesza B, Jonak K, Baj J, Grochowski C. Metformin as Potential Therapy for High-Grade Glioma. Cancers (Basel). 2020 Jan 15; 12(1): 210. https://doi.org/10.3390/cancers12010210

[16] Uchakina ON, Ban H, Hostetler BJ, McKallip RJ. Inhibition of hyaluronic acid formation sensitizes chronic myelogenous leukemia to treatment with doxorubicin. Glycobiology. 2016 Nov; 26(11): 1171-1179. https://doi.org/10.1093/glycob/cww064 Epub 2016 Jun 3.

[17] 2025 Merck & Co., Inc., Rahway, NJ, USA and its affiliates: Keytruda side effects https://www.keytruda.com/side-effects/

[18] Yates TJ, Lopez LE, Lokeshwar SD, Ortiz N, Kallifatidis G, Jordan A, Hoye K, Altman N, Lokeshwar VB. Dietary supplement 4-methylumbelliferone: an effective chemopreventive and therapeutic agent for prostate cancer. J Natl Cancer Inst. 2015 Apr 13; 107(7): djv085. https://doi.org/10.1093/jnci/djv085

[19] Zhang, W.; Yang, S.; Yu, X.; Zhu, S.; Wang, X.; Sun, F.; Liang, S.; Wang, X.; Zhao, G.; Gao, B. Beneficial Actions of 4-Methylumbelliferone in Type 1 Diabetes by Promoting β Cell Renewal and Inhibiting Dedifferentiation. *Biomedicines* 2024, *12*, 2790. https://doi.org/10.3390/biomedicines12122790

[20] Prehm P. Curcumin analogue identified as hyaluronan export inhibitor by virtual docking to the ABC transporter MRP5. Food Chem Toxicol. 2013 Dec; 62: 76-81. https://doi.org/10.1016/j.fct.2013.08.028

[21] Nagase H, Kudo D, Suto A, Yoshida E, Suto S, Negishi M, et al. 4-Methylumbelliferone Suppresses Hyaluronan Synthesis and Tumor Progression in SCID Mice Intra-Abdominally Inoculated With Pancreatic Cancer Cells. *Pancreas* (2017) 46(2): 190-7. https://doi.org/10.1097/MPA.0000000000000074

[22] Cosmin Stan M, Paul D. Diabetes and Cancer: A Twisted Bond. Oncol Rev. 2024 May 21; 18: 1354549. https://doi.org/10.3389/or.2024.1354549

[23] Tamura R, Yokoyama Y, Yoshida H, Imaizumi T, Mi zunuma H. 4-Methylumbelliferone Inhibits Ovarian Cancer Growth by Suppressing Thymidine Phosphorylase Expression. *J Ovarian Res* (2014) 7(1): 1-8. https://doi.org/10.1186/s13048-014-0094-2

[24] Heffler M, M. Golubovskaya V, Conroy J, Liu S, Wang D, G. Cance W, et al. FAK and HAS Inhibition Synergistically Decrease Colon Cancer Cell Viability and Affect Expression of Critical Genes. *Anticancer Agents Med Chem* (2013) 13(4): 584-94. https://doi.org/10.2174/1871520611313040008

[25] Nakazawa H, Yoshihara S, Kudo D, Morohashi H, Kakizaki I, Kon A, et al. 4-Methylumbelliferone, a Hyaluronan Synthase Suppressor, Enhances the Anticancer Activity of Gemcitabine in Human Pancreatic Cancer Cells. *Cancer Chemother Pharmacol* (2006) 57(2): 165-70. https://doi.org/10.1007/s00280-005-0016-5

[26] Sato N, Cheng XB, Kohi S, Koga A, Hirata K. Targeting Hyaluronan for the Treatment of Pancreatic Ductal Adenocarcinoma. *Acta Pharm Sin B* (2016) 6(2): 101-5. https://doi.org/10.1016/j.apsb.2016.01.002

[27] Chaudhry GE, Akim A, Naveed Zafar M, Safdar N, Sung YY, Muhammad TST. Understanding Hyaluronan Receptor (CD44) Interaction, HA-CD44 Activated Potential Targets in Cancer Therapeutics. Adv Pharm Bull. 2021 May; 11(3): 426-438. https://doi.org/10.34172/apb.2021.050

[28] Kubo, Hidemasa MD, PhD; Ohgi, Katsuhisa MD; Otsuka, Shimpei MD, PhD; Okawa, Yuta MD†; Ashida, Ryo MD, PhD; Yamada, Mihoko MD, PhD; Kato, Yoshiyasu MD, PhD; Dei, Hideyuki MD; Uesaka, Katsuhiko MD, PhD; Notsu, Akifumi PhD; Sugiura, Teiichi MD, PhD. Impact of Perioperative Hemoglobin A1C Levels on Survival Outcomes of Patients With Pancreatic Cancer: A Retrospective Study. Annals of Surgery Open 6(3): p e597, September 2025. |https://doi.org/10.1097/AS9.0000000000000597

[29] A Augustin, Ryan C. etal 2023 Frontiers in Oncology tumor micreoenvironment (TME), Melanoma, checkpoint blockade, Oxidative phoshorylation, Tumor infiltrating lymphocyte, Progression-free survival R https://doi.org/10.3389/fonc.2023.1075823

[30] Kim HS, Presti JC Jr, Aronson WJ, Terris MK, Kane CJ, Amling CL, Freedland SJ. Glycemic control and prostate cancer progression: results from the SEARCH database. Prostate. 2010 Oct 1; 70(14): 1540-6. https://doi.org/10.1002/pros.21189

[31] Rodríguez MM, Fiore E, Bayo J, Atorrasagasti C, García M, Onorato A, Domínguez L, Malvicini M, Mazzolini G. 4Mu Decreases CD47 Expression on Hepatic Cancer Stem Cells and Primes a Potent Antitumor T Cell Response Induced by Interleukin-12. Mol Ther. 2018 Dec 5; 26(12): 2738-2750. https://doi.org/10.1016/j.ymthe.2018.09.012

[32] Ferroni P, Formica V, Della-Morte D, Lucchetti J, Spila A, D'Alessandro R, Riondino S, Guadagni F, Roselli M. Prognostic value of glycated hemoglobin in colorectal cancer. World J Gastroenterol. 2016 Dec 7; 22(45): 9984-9993. https://doi.org/10.3748/wjg.v22.i45.9984

[33] Pembrolizumab/placebo plus paclitaxel with or without bevacizumab for platinum-resistant recurrent ovarian cancer (MK-3475-B96/KEYNOTE-B96/ENGOT-ov65). ClinicalTrials.gov. Updated March 7, 2025. Accessed May 15, 2025. https://www.clinicaltrials.gov/study/NCT05116189

[34] Merck announces phase 3 KEYNOTE-B96 trial met primary end point of progression-free survival (PFS) in patients with platinum-resistant recurrent ovarian cancer whose tumors expressed PD-L1 and in all comers. News release. Merck. May 15, 2025. Accessed May 15, 2025. https://tinyurl.com/5mawpz72

[35] Xu H, Niu M, Yuan X, Wu K, Liu A. CD44 as a tumor biomarker and therapeutic target. Exp Hematol Oncol. 2020 Dec 10; 9(1): 36. https://doi.org/10.1186/s40164-020-00192-0

[36] Li, William W. *Eat to Beat Disease: The New Science of How Your Body Can Heal Itself*. Grand Central Publishing, 201936.

[37] 1998-2025 Mayo Foundation for Medical Education and Research (MFMER). All rights reserved https://www.mayoclinic.org/drugs-supplements/metformin-oral-route/description/drg-20067074

[38] Štěpánková K, Mareková D, Kubášová K, Sedláček R, Turnovcová K, Vacková I, Kubinová Š, Makovický P, Petrovičová M, Kwok JCF, Jendelová P, Machová Urdzíková L. 4-Methylumbeliferone Treatment at a Dose of 1.2 g/kg/Day Is Safe for Long-Term Usage in Rats. Int J Mol Sci. 2023 Feb 14; 24(4): 3799. https://doi.org/10.3390/ijms24043799

[39] Weng, Xiong; Jiang, Hao; Walker, David J; Zhou, Houjiang; Deletion of CD44 promotes adipogenesis by regulating PPARγ and cell cycle-related pathways. *The Journal of endocrinology*, 30 Jun 2024, Vol. 262, Issue 1. https://doi.org/10.1530/JOE-24-0079

[40] Chen, Dongjiang Efficacy and safety of adjuvant TTFields plus pembrolizumab and temozolomide in newly diagnosed glioblastoma: A phase 2 study Cell Press Journal ArticleVolume 6, Issue 9100708 September 12, 2025 https://doi.org/10.1016/j.medj.2025.100708

[41] Fusco, M.; Picón, C. R.; Diaz, M. A.; Bayo, J.; Arriola Benitez, P. C.; Piccioni, F.; Gómez, N.; Stinco, M.; Martínez Martinez, J.; Minatta, J. N.; et al. 4-Methylumbelliferone Modulates CAIX to Mitigate Hypoxia-Driven Dysregulation and Enhance PD-1 Immunotherapy in Lung Cancer. *Int. J. Mol. Sci.* 2025, *26*, 10427. https://doi.org/10.3390/ijms262110427

[42] Merk, KEYNOTE-189 January 16, 2018 KEYTRUDA is First PD1 Inhibitor in Combination to Show Overall Survival in NSCLC.

[43] Merck KEYNOTE-641 February 28, 2023Provides Update on Phase 3 Trials KEYNOTE-641 and KEYNOTE-789

[44] Nagy N, Czepiel KS, Kaber G, Stefanovski D, Hargil A, Pennetzdorfer N, Targ R, Reghupaty SC, Wight TN, Vernon RB, Hull-Meichle RL, Marshall P, Medina CO, Martinez H, Kalinowski A, Paladini RD, Garantziotis S, Knowles JW, Bollyky PL. Hymecromone Promotes Longevity and Insulin Sensitivity in Mice. Cells. 2024 Oct 18; 13(20): 1727. https://doi.org/10.3390/cells13201727

[45] Kulesa, PM, Kasemeier-Kulesa, JC, Teddy, JM, Margaryan, NV, Seftor, EA, et al. (2006). Reprogramming Metastatic Melanoma Cells to Assume a Neural Crest Cell-like Phenotype in an Embryonic Microenvironment. Proc Natl Acad Sci U S A 103(10): 3752-3757.

[46] Seki, T., Yang, Y., Sun, X. *et al.* Brown-fat-mediated tumor suppression by cold-altered global metabolism. *Nature* 608, 421-428 (2022). https://doi.org/10.1038/s41586-022-05030-3

[47] American Cancer Society, Inc. “What is lung Cancer?” 2025.

[48] Kong M, Lim YJ. Chronic hyperglycemia is an adverse prognostic factor for locoregional recurrence-free survival in small cell lung cancer patients treated with radical radiotherapy. Thorac Cancer. 2022 Sep; 13(18): 2633-2640. https://doi.org/10.1111/1759-7714.14601 Epub 2022 Aug 4.

Biography

John Claras, Independent Researcher Sunnyvale, CA The original concept of “the Pragmatic Switch” was proposed in 2011 at a youth soccer game. The blog describing the initial concept appeared in 2016. This is the 4rd in a series of papers to define the cancer model and now offer a possible treatment.