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*Review*

# Synergy of Combining Methionine Restriction and Chemotherapy: The Disruptive Next Generation of Cancer Treatment

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**Abstract.** *All cancer cell types are methionine-addicted, which is termed the Hoffman effect. Cancer cells, unlike normal cells, cannot survive without large amount of methionine. In general, when methionine is depleted, both normal cells and cancer cells synthesize methionine from homocysteine, but cancer cells consume large amounts of methionine and they cannot survive without exogenous methionine. For this reason, methionine restriction has been shown to be effective against many cancers in vitro and in vivo. Methionine restriction arrests cancer cells in the S/$G_2$-phase of the cell cycle. Cytotoxic agents that act in the S/$G_2$-phase are highly effective when used in combination with methionine restriction due to the cancer cells being trapped in S/$G_2$-phase, unlike normal cells which arrest in $G_1$/$G_0$-phase. Combining methionine restriction and chemotherapeutic drugs for cancer treatment is termed the Hoffman protocol. The efficacy of many cytotoxic agents and molecular-targeted drugs in combination with methionine restriction has been demonstrated. The most effective method of methionine restriction is the administration of recombinant methioninase (rMETase), which degrades methionine. The efficacy of rMETase has been reported in mice and human patients by oral administration. The present review describes studies on anticancer drugs that showed synergistic efficacy in combination with methionine restriction, including rMETase administration. It is proposed that the next disruptive generation of cancer chemotherapy should employ current therapy in combination with methionine restriction for all cancer types.*

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Methionine dependence of cancer was discovered by Sugimura *et al*. in 1959 (1) when it was observed that methionine-depleted rat chow slowed cancer growth in rats more than chow depleted of other amino acids. Fourteen years later, Chello and Bertino (2) found that leukemia and lymphoma cells could not grow in culture, while normal cells could grow, when methionine was replaced by its immediate precursor, homocysteine.

In 1976, we found that cancer cells make normal or large amount of methionine, but still usually require an exogenous source of methionine (3). The conclusion was that cancer cells are addicted to methionine. Wang *et al*. 43 years later, confirmed that cancer cells are addicted to methionine, especially tumor-initiating or stem cells (4).

We originally showed that cancer cells were methionine-addicted, at least in part due to elevated transmethylation reactions (5), with histone lysine marks being over-methylated in cancer (6–9). Rare revertant of cancer cells

that have regained methionine independence, have reduced levels of transmethylation (10, 11), have lost their malignancy (7-9), and do not necessarily increase their ability to make methionine from homocysteine (12).

The methionine addiction of cancer is known as the Hoffman effect. Comparison of [$^{11}$C]methionine positron emission tomography (PET) and [$^{18}$F]deoxyglucose PET has shown that the Hoffman effect is more pronounced than the Warburg effect of cancer addiction to glucose (13).

We first observed selective cell-cycle arrest of cancer cells in S/$G_2$-phase when they are depleted of methionine (14). The S/$G_2$-phase of the cell cycle is the vulnerable point of cytotoxic chemotherapy, resulting in the possibility of synergy. We first observed this synergy almost 40 years ago when normal and cancer cells were co-cultured with the combination of methionine restriction and chemotherapy, which could selectively eliminate all the cancer cells, leaving healthy intact normal cells (15). Subsequently, we have shown synergy of all major types of chemotherapy and methionine restriction, including with recombinant methioninase (rMETase). We believe that the next disruptive generation of cancer treatment will combine methionine restriction and current chemotherapy.

## Doxorubicin (DOX) Synergy With Methionine Restriction

The first chemotherapeutic drug that showed a synergistic effect with methionine restriction was doxorubicin (DOX). As mentioned above, cancer cells become reversibly blocked in the late S/$G_2$-phase under methionine depletion (14). DOX blocks topoisomerase 2 and targets S-phase and was predicted to be synergistic with methionine restriction. Stern *et al*. (15) demonstrated the synergistic effect of methionine restriction and DOX using sarcoma, prostate cancer, lung cancer, and breast cancer cell lines co-cultured with normal fibroblasts. Homocysteine was substituted for methionine in the culture medium and DOX was then added. After administering DOX to the cancer cells that had been arrested in S/$G_2$-phase by methionine restriction, methionine was added to stimulate the cancer cells to synchronously resume cycling and then vincristine was added, which acts in M-phase to kill the cancer cells entering mitosis. Normal cells were protected because they arrest in $G_0$-phase when methionine-depleted. This disruptive strategy resulted in selectively eliminating all the cancer cells from the co-culture, leaving a healthy culture of normal fibroblasts (15) (Table I).

Gupta *et al*. showed the efficacy of the combination of DOX and methioninase, using a recombinant adenovirus (Ad-MET) which produced methioninase, on the human lung-cancer cell line H460 (16). Selenomethionine (SeMET), which is degraded by methioninase and results in the highly toxic methylselonol that has a strong bystander effect, was also added as a pro-drug. The combination treatment of DOX, Ad-MET, and SeMET inhibited tumor growth more than the combination of Ad-MET and SeMET.

Recently, the synergistic efficacy of the combination of DOX and recombinant methioninase (rMETase) (oral or intraperitoneal dosing) was reported in synovial sarcoma (17, 18) and undifferentiated spindle-cell carcinoma (19, 20) in patient-derived orthotopic xenograft (PDOX) mouse models (Table I).

A patient with invasive lobular carcinoma of the breast who received DOX and cyclophosphamide combined with rMETase and a low-methionine diet had her axillary-lymph-node metastasis eliminated (21) (Table I).

## 5-Fluorouracil (5-FU) Synergy With Methionine Restriction

5-Fluorouracil (5-FU) is an anti-metabolite that targets cells in the S-phase of the cell cycle similar to DOX. Hoshiya *et al*. (22) originally showed the synergistic efficacy of the combination of methionine restriction and 5-FU using the human gastric-cancer cell-line (SC-1-NU) xenograft mouse model. This study demonstrated that methionine restriction enhanced the antitumor activity of 5-FU by approximately two-fold. Hoshiya *et al*. also showed that methionine restriction increased intra-tumoral thymidylate-synthase (TS) inhibition by 5-FU. Recently, Gao *et al*. (23) showed that methionine restriction combined with 5-FU enhanced the treatment response in RAS-driven colorectal cancer in patient-derived xenograft (PDX) models, confirming the original result of Hoshiya *et al*. (22) (Table I).

A clinical trial for gastric cancer patients was performed using 5-FU combined with methionine-free total parenteral nutrition (TPN) (24). Fourteen patients with gastric cancer who had stenosis or obstruction of the gastric canal were registered in this trial. The patients were randomly allocated into two groups, 5-FU and methionine-free TPN, or 5-FU and normal (methionine-containing) TPN. All patients received surgery after 7 days of 5-FU and TPN. The specimens in the methionine-free TPN group showed extensive degeneration of cancer. Also, the TS activity was decreased in the tumor in the methionine-free TPN group (Table I).

Subsequently, the synergistic efficacy of the combination of 5-FU and rMETase was shown using a xenograft model of Lewis lung carcinoma cells, including extended survival (25). Machover *et al*. demonstrated the efficacy of adding folinic acid to 5-FU and rMETase on the CCRF-CEM human T-lymphoblastic leukemia cell line *in vitro* (26). The synergistic efficacy of 5-FU and oral rMETase was observed in colorectal cancer, poorly-differentiated gastric cancer, and colon-cancer peritoneal-carcinomatosis mouse models (27–29) (Table I).

Lu *et al*. (30) showed that methionine restriction combined with 5-FU reduced 5,10-methylene-tetrahydrofolate levels by 75% and selectively inhibited TS activity in PC-3 human prostate-cancer cells. Reduction of 5,10-methylene-tetrahydrofolate decreased the level of 5-methyl-tetrahydrofolate, which is necessary for methionine synthesis. 5,10-methylene-tetrahydrofolate depletion and decreased TS activity, due to methionine restriction, resulted in synergistic efficacy with 5-FU (30) (Table I).

## Gemcitabine (GEM) Synergy With Methionine Restriction

Gemcitabine (GEM) is also classified as an anti-metabolite targeting cells in S-phase. The synergistic efficacy of GEM and rMETase (intraperitoneal and oral dosing) was reported in PDOX and orthotopic cell-line mouse models of pancreatic cancer (31, 32). These studies showed that the combination of GEM and rMETase was synergistically effective for GEM-resistant pancreatic cancer. GEM resistance can be overcome by using methionine restriction in combination with the drug to which the cancer cells are resistant (Table I).

## Methotrexate (MTX) Synergy With Methionine Restriction

MTX is also classified as an anti-metabolite. MTX inhibits dihydrofolate reductase (DHFR) and methylene-tetrahydrofolate reductase (MTHFR), which decrease the level of 5-methyl-tetrahydrofolate that adds a methyl group to homocysteine, and therefore blocks endogenous methionine production (33). MTX also inhibits methionine S-adenosyltransferase (MAT). MTX, combined with rMETase, was therefore synergistic on an MTX-resistant osteosarcoma PDOX model (33) (Table I).

## Platinum-based Chemotherapy Synergy With Methionine Restriction

Platinum agents, such as cisplatinum and oxaliplatinum bind to nuclear DNA and subsequently interfere with DNA replication. Hoshiya *et al*. originally demonstrated the synergistic efficacy of cisplatinum and methionine restriction *in vitro* and on a xenograft mouse model utilizing the human breast cancer cell line MX-1 (34). In addition, cisplatinum combined with rMETase showed efficacy for colon cancer cell lines (Colo205, SW620, HCT15, and HT29) xenograft mouse models (35), and osteosarcoma PDOX and orthotopic xenograft mouse models (36–38), and a bladder-cancer orthotopic mouse model (39).

Oxaliplatinum is used for colon cancer combined with 5-FU because its monotherapy is not effective in clinical settings. This combination is termed FOLFOX. FOLFOX showed synergistic efficacy combined with oral rMETase in a colon-cancer PDOX mouse model (27) and orthotopic xenograft mouse model (29).

A clinical trial was performed using the combination of a low-methionine diet and FOLFOX. This trial included 11 patients with unresectable colorectal cancer. From the start of chemotherapy, all patients were on a methionine-free diet for three days. Of the 4 patients evaluable for response, 3 experienced a partial response, and 1 patient had stable disease (40). Recently, a case of a patient with stage IV pancreatic cancer who received oxaliplatinum with 5-FU and irinotecan, which is termed FOLFIRINOX, combined with a low-methionine diet and rMETase, has 18 months of stable disease, a result found in only 5% of stage IV pancreatic cancer patient (41) (Table I).

## Alkylating Agents Synergy With Methionine Restriction

Kokkinakis *et al*. showed the synergistic efficacy of alkylating agents [carmustine (BCNU) and temozolomide] and methionine restriction in brain-cancer xenograft mouse models, using rMETase and low-methionine mouse chow, including Daoy (medulloblastoma), SWB77 (glioblastoma), and D-54 (glioblastoma) (42). In general, glioblastomas with MGMT activation are resistant to temozolomide. However, methionine restriction decreased MGMT activation (42). Therefore, temozolomide with methionine restriction is effective against glioblastoma, even if MGMT is activated. The synergistic efficacy of temozolomide and intraperitoneal rMETase was also reported in a *BRAF* mutant melanoma PDOX mouse model (43).

The combination of cystemustine and a methionine-restricted diet was examined in human phase 1 and 2 trials for melanoma and high-grade glioma patients (44, 45). In the phase 2 trial, the period of methionine restriction was set to only one day for each two-week cystemustine cycle, based on the results of the phase 1 trial. The results of these trials showed that this combination of cystemustine and methionine restriction has less toxicity, but no efficacy, compared to historical controls. One-day methionine restriction is too short a period for depleting methionine (Table I).

## Tubulin-targeting Drugs Synergy With Methionine Restriction

Taxanes, such as paclitaxel and docetaxel, as well as eribulin, a halichondrine, affect the M-phase of the cell cycle by interfering with microtubules. Cancer cells that escape the $S/G_2$ cell-cycle block induced by methionine restriction are then killed by tubulin-targeting drugs as they enter M-phase.

Table I. *Synergy of methionine restriction and chemotherapy.*

| Chemotherapy drug | Type of methionine restriction | Model | Result | Reference |
|---|---|---|---|---|
| Doxorubicin (+ vincristine) | MET-free medium | Co-culture; sarcoma (HOS-1A), Prostate cancer (PC1C), Lung cancer (A2182-5D), Breast cancer (MCF-7), with Fibroblasts (FS-3) | Selective elimination of cancer cells | Stern PH *et al*. (15) |
| Doxorubicin (+ seleno-MET) | Cancer cells transfected with Ad-MET | Cell culture; Lung cancer (H460)<br>Subcutaneous cell-line mouse model; Lung cancer (H460) | Cell-growth inhibition<br>Tumor-growth inhibition | Gupta A *et al*. (16) |
| Doxorubicin | Intraperitoneal rMETase | Synovial sarcoma PDOX | Tumor-growth inhibition | Igarashi K *et al*. (17) |
| Doxorubicin | Oral rMETase | Synovial sarcoma PDOX | Tumor-growth inhibition | Higuchi K *et al*. (18) |
| Doxorubicin | Intraperitoneal rMETase | Undifferentiated spindle-cell sarcoma | Tumor-growth inhibition | Igarashi K *et al*. (19, 20) |
| Doxorubicin (+ cyclophosphamide) | Oral rMETase, low-MET diet | Breast cancer patient (ILC) | Metastases elimination | Kubota K *et al*. (21) |
| 5-FU | Low-MET diet | Orthotopic cell-line mouse model; Gastric cancer (SC-1-NU) | Tumor growth inhibition | Hoshiya Y *et al*. (22) |
| 5-FU | Low-MET diet | Colorectal-cancer PDX | Tumor-growth inhibition | Gao X *et al*. (23) |
| 5-FU | MET-free TPN | Gastric-cancer patients | Histological down grade | Goseki N *et al*. (24) |
| 5-FU | Intraperitoneal rMETase | Subcutaneous cell-line mouse model; Lung cancer (Lewis lung carcinoma) | Tumor-growth inhibition<br>Prolongation of survival | Yoshioka T *et al*. (25) |
| 5-FU (+ folinic acid) | rMETase | T-lymphoblastic leukemia cells | Cell toxicity | Machover D *et al*. (26) |
| 5-FU (+ oxaliplatinum) | Oral rMETase | Colorectal-cancer PDOX | Tumor-growth inhibition | Oshiro H *et al*. (27) |
| 5-FU | Oral rMETase | Subcutaneous cell-line mouse model; Gastric cancer (MKN45) | Tumor-growth inhibition | Miyake M *et al*. (28) |
| 5-FU (+oxaliplatinum) | Oral rMETase | Peritoneal-metastasis cell-line mouse model; Colon cancer (HCT-116) | Prolongation of survival | Kim M *et al*. (29) |
| 5-FU | Low-MET medium | Cell culture; Prostate cancer (PC-3) | Cell-growth inhibition, inhibit TS | Lu S *et al*. (30) |
| Gemcitabine | Intraperitoneal rMETase | Pancreatic-cancer PDOX | Tumor-growth inhibition | Kawaguchi K *et al*. (31) |
| Gemcitabine | Oral rMETase | Gemcitabine-resistant orthotopic pancreatic cell-line mouse model | Tumor-growth inhibition | Kawaguchi *et al*. (32) |
| Methotrexate | Oral rMETase | Osteosarcoma PDOX | Tumor-growth inhibition | Aoki Y *et al*. (33) |
| Cisplatinum | Low-MET diet | Subcutaneous cell-line mouse model; Breast cancer (MX-1) | Tumor-growth inhibition | Hoshiya Y *et al*. (34) |
| Cisplatinum | rMETase<br>Intraperitoneal rMETase | Cancer cell culture; Colon cancer (Colo205, SW620)<br>Subcutaneous cell-line mouse model; Colon cancer (HT29, HCT15, Colo205, SW620) | Cell-growth inhibition<br>Tumor-growth inhibition | Tan Y *et al*. (35) |
| Cisplatinum | Intraperitoneal rMETase | Osteosarcoma PDOX | Tumor-growth inhibition | Igarashi K *et al*. (36) |
| Cisplatinum | Oral rMETase | Osteosarcoma PDOX | Tumor-growth inhibition<br>Overcome cisplatinum resistance | Higuchi T *et al*. (37) |
| Cisplatinum | Oral rMETase | Osteosarcoma-of-the-mammary-gland PDOX | Tumor-growth inhibition | Masaki N *et al*. (38) |
| Cisplatinum | Oral rMETase | Bladder-cancer orthotopic mouse model | Tumor-growth and metastasis inhibition | Sun et al. (39) |
| Oxaliplatinum (+ 5-FU) | Oral rMETase | Colorectal-cancer PDOX | Tumor-growth inhibition | Oshiro H *et al*. (27) |
| Oxaliplatinum (+ 5-FU) | Oral rMETase | Peritoneal-metastasis cell-line mouse model; Colon cancer (HCT-116) | Prolongation of survival | Kim M *et al*. (29) |
| Oxaliplatinum (+ 5-FU) | MET-free diet | Colon-cancer patients | Disease control | Durando X *et al*. (40) |
| Oxaliplatinum (+ 5-FU + irinotecan) | Low-MET diet + Oral rMETase | Pancreatic-cancer patient | Disease control | Kubota Y *et al*. (41) |
| BCNU<br>Temozolomide | Low-MET diet + intraperitoneal rMETase | Subcutaneous cell-line mouse model; Glioblastoma (SWB77, D-54), medulloblastoma (Daoy) | Tumor-growth inhibition | Kokkinakis DM *et al*. (42) |
| Temozolomide | Intraperitoneal rMETase | BRAF V600E melanoma PDOX | Tumor-growth inhibition | Kawaguchi K *et al*. (43) |
| Cystemustine | Low-MET diet | Melanoma or high-grade glioma patients (Phase 1, 2) | No effect compared to historical controls | Durando X and *et al*. (44) Thivat E et al. (45) |

Table I. *Continued*

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| Chemotherapy drug | Type of methionine restriction | Model | Result | Reference |
|---|---|---|---|---|
| Paclitaxel | Oral rMETase | Ovarian clear-cell-carcinoma PDOX | Tumor-growth inhibition | Sugisawa N *et al*. (46) |
| Eribulin | Oral rMETase | Triple negative breast cancer liver-metastasis PDOX | Tumor-growth inhibition | Lim H *et al*. (47) |
| Docetaxel | Oral rMETase | Docetaxel-resistant osteosarcoma PDOX | Tumor-growth inhibition<br>Overcome docetaxel-resistance | Aoki Y *et al*. (48) |
| Tamoxifen | rMETase<br>Oral rMETase | Cell culture; Breast cancer (MCF-7)<br>Orthotopic cell-line mouse model; Breast cancer (MCF-7) | Cell-growth inhibition<br>Tumor-growth inhibition | Kavya D *et al*. (48) |
| Palbociclib | Intraperitoneal rMETase | Doxorubicin-resistant dedifferentiated-liposarcoma PDOX | Tumor-growth inhibition | Igarashi K *et al*. (50) |
| Azacytidine | Oral rMETase | Chemotherapy-resistant osteosarcoma PDOX | Tumor-growth inhibition | Higushi T *et al*. (53) |
| Decitabine | Oral rMETase | Chemotherapy-resistant undifferentiated soft-tissue sarcoma | Tumor-growth inhibition | Higuchi T *et al*. (51) |
| Azacytidine (+ cycloleucine) | Oral rMETase | Pancreatic-cancer PDOX | Tumor-growth inhibition | Sugisawa N *et al*. (54) |
| Rapamycin | Oral rMETase | Osteosarcoma-of-the-breast PDOX | Tumor-growth inhibition | Masaki N *et al*. (56) |
| Tigatuzumab | rMETase | Cell culture; Pancreatic cancer | Cell-growth inhibition | Yamamoto J *et al*. (58) |
| Lexatumumab | Oral rMETase<br>Low-methionine diet | (MIA PaCa-2, BxPC-3); Triple-negative breast cancer (MDA-MB-231)<br>Orthotopic cell-line mouse model: Pancreatic cancer (MIA PaCa-2) and triple-negative breast cancer (MDA-MB-468) | Tumor-growth inhibition | Strekalova *et al*. (57) |
| Auranofin (Anti-oxidant inhibitor) | Low-methionine medium or diet | Breast cancer cells in culture, orthotopic mouse model | Cell-growth and tumor-growth inhibitor | Malin *et al*. (74) |

MET: Methionine; Ad-MET: recombinant adenoviral vector with the methioninase gene; rMETase: recombinant methioninase; PDOX: patient-derived orthotopic xenograft; ILC: invasive lobular carcinoma; 5-FU: 5-fluorouracil; PDX: patient-derived xenograft.

Paclitaxel for clear-cell ovarian cancer (46), eribulin for triple-negative cancer (47), and docetaxel for osteosarcoma (48) were synergistic with oral rMETase in PDOX mouse models (Table I).

## Tamoxifen Synergy With Methionine Restriction

Tamoxifen, a hormone analog that inhibits the estrogen receptor, showed synergistic efficacy with rMETase in a breast-cancer orthotopic xenograft mouse model (MCF-7) (49). The combination of rMETase and tamoxifen increased caspase-3 and -8 expression, indicating apoptosis. The mechanism of the synergy of this combination is not clear (Table I).

## Palbociclib Synergy With Methionine Restriction

Palbociclib is a cyclin-dependent kinase (CDK)-4 and -6 inhibitor (50). This blockade inhibits the progress of the cell cycle from the $G_1$-phase to the S-phase. In a PDOX mouse model of DOX-resistant dedifferentiated liposarcoma, the synergistic efficacy of palbociclib and rMETase was demonstrated (50). These results show that the double blockade of the cell cycle (phases $G_1$ to S and S to $G_2$) is effective against cancer cells (Table I).

## DNA-methylation-inhibitor Synergy With Methionine Restriction

Azacytidine and decitabine are classified as hypo-methylating agents. They prevent the methylation of the cytosines in DNA by inhibiting DNA methyltransferase (51). Methionine restriction decreases S-adenosylmethionine (SAM) (52), which is the only methyl-group provider for DNA, RNA, and histone methylation. In osteosarcoma and soft-tissue sarcoma PDOX mouse models, the combination of azacytidine or decitabine and rMETase was synergistically effective (51, 53). Another PDOX mouse model study using pancreatic cancer demonstrated the synergistic efficacy of rMETase, azacytidine, and cycloleucine, which is a specific inhibitor of SAM synthesis (54). Further study is needed to investigate the effect of methionine restriction on DNA methylation (Table I).

## Rapamycin Synergy With Methionine Restriction

Rapamycin targets mTOR kinase and inhibits the PI3K/AKT signaling pathway (55). The synergistic efficacy of rapamycin and oral rMETase was reported in an osteosarcoma- of-the-breast PDOX mouse model (56) (Table I).

## Targeting TRAIL Receptor-2 Synergy With Methionine Restriction

Tigatuzumab and lexatumumab target TNF-related apoptosis-induced ligand receptor-2 (TRAIL-R2) (57, 58). Methionine restriction increased TRAIL-R2 expression in cancer cells. Lexatumumab inhibited triple-negative breast cancer *in vitro* and in mice with low-methionine medium or diet. Tigatuzumab combined with oral rMETase showed synergy on pancreatic-cancer orthotopic xenograft mouse models (MIA PaCa-2 and BxPC-3) (58) (Table I).

## Discussion

It was first shown by Sugimura *et al*. in 1959 (1) that cancers are methionine-dependent and subsequently Hoffman and Erbe showed cancers are methionine-addicted in 1976 (3). It was then shown that all cancers are methionine addicted (59, 60). As described in the present report, many mouse experiments and human studies have shown the synergy of different anticancer drugs with methionine restriction. Anti-metabolites, DOX, alkylating agents, and platinum drugs target cells in S/$G_2$-phase where cancer cells are selectively blocked by methionine restriction (14, 28, 61). In addition, methotrexate and 5-FU target folate metabolism, and therefore decrease the ability of cells to synthesize methionine, and show synergistic efficacy with methionine restriction. Methotrexate was shown to increase histone-lysine methylation in cancer cells, which alters cell programming (62). Other cytotoxic and molecular-targeting agents such as taxanes, tamoxifen, palbociclib, azacytidine, rapamycin, and tigatuzumab are also synergistic with methionine restriction.

In an emerging series of human studies (21, 41), rMETase appears synergistic with chemotherapy. No side effects related to methionine restriction have been shown in either mouse or human studies.

The next disruptive generation of cancer treatment will be based on combining methionine restriction with current chemotherapy. which is termed the Hoffman protocol (56).

It should be noted that methionine addicted cancer cells are also addicted to folate (63) which contributes to the efficacy of anti-folate chemotherapy (33).

Despite overwhelming evidence that cancer cells express high levels of methionine synthase (3,4,64,65), misinformation published 50 years ago that methionine dependence of cancer is due to depleted methionine synthase (66, 67) still persists (68).

Very recently a paper published in Nature (69) showed research is becoming less disruptive. This seems not to be the case for the next generation of cancer chemotherapy based on methionine addiction of cancer (3-11, 13, 52, 70-73).

Emerging evidence suggests that methionine restriction sensitizes cancer cells to pro-oxidants (Table I) (74).

## Conflicts of Interest

The Authors declare no competing interests regarding this work.

## Authors' Contributions

YK and RMH wrote the article. QH provided the recombinant methioninase. YA, NM, KO, KH, CH, AW, MB, and TT reviewed the article.

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