**Mitchell Ghen Integrative Cancer meeting NOVA June July Aug 2021 Case Study-Final Exam**

74-year-old black male, diagnosed with renal cancer; subsequently had a right nephrectomy

15 years later developed metastatic lesions in his lungs and undergoes chemotherapy

His medications include Valsartan, Amlodipine, Doxazosin, Lasix, Atorvastatin

PE: Corrective lenses, 2/6 systolic ejection murmur, abdomen enlarged, no ascites palpated

Blood tests revealed the following pertinent findings:

Urinary Vitamin C level: extremely low

Urine protein 4+

Malondialdehyde 6 on o scale 0-7 (0=best, 7= worst)

Homocysteine 42 umol/L

NT-proBNP 1479 (<300 pg/mL is normal)

GGT 102 (3-70 U/L is normal)

EBV Early-D Antigen >150 (<9 U/mL is normal)

Iodine 49 mcg/L (50-109 mcg/L is normal)

WBC 2.4 Thousand/uL

Hgb 10 g/dL

Hct 31.6 %

Pregnenolone 12ng/dL

DHEA-S 73 mcg/dL

Testosterone total 198 ng/dL

Testosterone free 26.1 pg/mL (6-73 pg/mL is normal)

CEA 4.2 ng/mL (<2.5 ng/mL is normal)

CRP HS 34 mg/L

Fibrinogen activity 411 mg/dL

Cholesterol total 91 mg/dL

BUN 60 mg/dL

Creatinine 7.02 mg/dL

Calcium 8.4 mg/dL

Albumin 3.4 gm/dL

Hgb A1C 4.8

Uric acid 9.9 mg/dL

Vitamin D-25 OH 35 ng/mL

LDH 1 and LDH 2 are low

LDH 4 is high

Develop a comprehensive repurposed drugs and natural substances program for this patient.

Email your completed protocol to drmitch@mitchghen.com by September 14th 2021.

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Clear Cell Renal Carcinoma (RCC) is highly Glycolytic, has minimal mitochondrial capacity and is highly sensitive to Glycolysis inhibitors such as DCA, Fenbenzadole, Quercetin etc. (1-10)

**Role of PET Scan in RCC**

Because of the highly Glycolytic nature of RCC, PET scanning is very a useful imaging modality to monitor disease progression. (43-45) (79)

**HIF inhibitors**

HIF (Hypoxia Inducing Factor) activation is another key pathway activated in RCC , inhibited by Allicin (81) and Thymoquinone (Black Seed Oil) which has been extensively studied in RCC and is a HIF inhibitor and is effective for RCC. (34-36) Thymoquinone is also renoprotective (37-39)

**RCC is Highly GLYCOLYTIC and responds to GLYCOLYSIS inhibitors**

Targeting GLUT1 and MCT4 are valid anti-cancer strategies. (56-66)

Quercetin is a known MCT inhibitor, and alters AKT/mTOR/ERK signalling pathway. (69)(97)

3BP (research only) is another Glycolysis inhibitor effective for RCC (82)

**Silybin Blocks GLUT Transporters**

Silybin (Milk Thistle) blocks the activity of the GLUT transporter proteins , reduces glucose uptake and inhibits Glycolysis. (16) Silybin also blocks EGFR-ERK activation, inhibits EMT, g, downregulates mTOR and BCL2, and induces “protective autophagy” in RCC (17-

22)

**RCC has Upregulated EGF Epidermal Growth Factor**

Solomon’s Seal PCL is a potent EGF inhibitor and would be useful in RCC. (77-78)(78a)

“The plant lectin, Solomon’s seal (PCL), has remarkable anti-cancer activities as a potent EGFR inhibitor. In addition, PCL is taken up and accumulates in mitochondria, depletes glutathione, and generates massive reactive oxygen species (ROS), which then induces both protective autophagy and mitochondrial apoptosis. Solomon ’s seal is widely available as a plant extract nutritional supplement.” (Quote from Cracking Cancer Toolkit, Chapter on Solomon’s Seal)

**Fenbendazole for RCC - Veterinary Use Only**

A veterinary antiparasitic, Fenbendazole, although not approved for human use, is an excellent glycolysis inhibitor has been used by humans and three case reports show dramatic regression in renal cell carcinoma. (15)

**Cordyceps Anti-inflammatory and Reno Protective**

Cordyceps inhibits the NF-kB pathway and is effective in RCC in numerous studies.(23-30)

Cordyceps is also reno-protective which is important in post-nephrectomy RCC patients who have only one kidney with elevated BUN and Creatinine. Cordyceps also inhibits platelet aggregation. (31-33)

**Melatonin**

Melatonin reverses the Warburg effect and has no adverse side effects and has been studied and is effective in RCC. (11-13)

**Mifepristone for RCC**

Case report by Dr Jerome Check of a patient with bilateral renal cell CA treated with heminephrectomy. Patient survived 12 years on Mifepristone with no adverse side effects. (101)

**Vitamin D3 - Hedgehog Pathway Re-Activated in RCC**

Vitamin D3 and Resveratrol (Pterostilbene) targets HH pathway in RCC (110)(112) Pterostilbene is effective for RCC and is reno-protective. (41-42) Itraconazole is another well known Hedgehog pathway inhibitor. (111)

EGCG Green Tea is effective for RCC (103-107)

**Oxaloacetate/ RCC has a Glutamine Addiction**

The “Achilles Heel” of metabolism in RCC is Glutamine Addiction. (46-51) This suggests utility of treatment with oxaloacetate for RCC. In addition, oxaloacetate enhances OXPHOS and Inhibits GLYCOLYSIS (Warburg effect). Since RCC has a high level of GLYCOLYSIS, treatment with Oxaloacetate should be effective. (52)

**RCC is Stimulated by Erythropoietin**

Therefore, use of Procrit (recombinant erythropoietin), or testosterone, which increases erythropoietin is contraindicated in RCC.(54-55)

**Avoid Agents that Impair Renal Function**

Many RCC patients have had nephrectomies with rising BUN and creatinine. Fenofibrate can increase serum creatinine in renal insufficiency. Avoid it. (70-73) Similarly Diclofenac and other NSAIDS may impair renal function.

**CIMETIDINE for RCC**

Cimetidine 800 mg was effective for two patients with metastatic RCC (83-84)

Atovaquone OXPHOS Inhibitor may sensitize RCC to chemotherapy (85-89)

Sulforaphane may be useful in RCC (90-93) In addition, sulphoraphane is renoprotective(94-96)

Artesunate may be a useful treatment strategy. (98)

Niclosamide exhibits potent anti cancer activity and synergizes with sorafenib in RCC. (99-100)

Hydroxychloroquine -Autophagy Inhibitor as add-on in RCC (114-116)

Curcumin inhibits NFkB anti-inflammatory properties. (80)

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**References for Renal Cell Carcinoma Repurposed Drugs**

1) Haque, Inamul, et al. “The role of compounds derived from natural supplement as anticancer agents in renal cell carcinoma: a review.” International journal of molecular sciences 19.1 (2018): 107.

2) Nabi, Shahzaib, et al. “Renal cell carcinoma: a review of biology and pathophysiology.” F1000Research 7 (2018).

3) Lameirinhas, Ana, et al. “The complex interplay between metabolic reprogramming and epigenetic alterations in renal cell carcinoma.” Genes 10.4 (2019): 264.

Glycolysis Inhibitor 3BP

4) Primary clear cell renal carcinoma cells display minimal mitochondrial respiratory capacity resulting in pronounced sensitivity to glycolytic inhibition by 3-Bromopyruvate H Nilsson,1

Decreased Mitochondria DNA

5) Meierhofer, David, et al. “Decrease of mitochondrial DNA content and energy metabolism in renal cell carcinoma.” Carcinogenesis 25.6 (2004): 1005-1010.

Decreased OXPHOS

6) Simonnet, Hélène, et al. “Low mitochondrial respiratory chain content correlates with tumor aggressiveness in renal cell carcinoma.” Carcinogenesis 23.5 (2002): 759-768.

All results are in agreement with the hypothesis that a decreased OXPHOS capacity favors faster growth or increased invasiveness.

DCA Key article !!!!

7) Kinnaird, Adam. “Metabolic Reprogramming and Epigenetic Regulation in Renal Cell Carcinoma.” (2018). pdf

We show that reversing the suppression of mitochondrial glucose oxidation in ccRCC using dichloroacetate, an inhibitor of the HIF target gene mitochondrial pyruvate dehydrogenase kinase (PDK), which inhibits a major producer of acetyl-CoA, the Pyruvate Dehydrogenase Complex (PDC), results in increased production of mitochondrial acetyl-CoA via PDC, reduced proliferation and angiogenesis, and induces apoptosis in animal models.

Although the initial half-life of DCA is very short (i.e. approximately 2

hours) [96], the drug inhibits its own metabolism until it reaches a plateau, and thus therapeutic concentrations can be achieved in plasma with time (for example, at a dosing regime of 6.25mg/kg x 80 kg = 500 mg twice a day for three months) = 500 mg BID

DCA’s proven ability to increase the GO/glycolysis ratio in the treated

tumors and its ability to decrease **HIF1α** activity and thus reverse the up-

regulation of glucose transporters, suggest that metabolic imaging, like FDG-PET maybe used to track its effects in vivo, a very desirable tool in drug development.

DCA

8) Kalay, Saban, et al. “Dicholoroacetate exerts anti-cancer activity on human renal cell carcinoma cells.” Turkish Journal of Biochemistry 42.5 (2017): 577-585.

9) Khan, Akbar. “Case report of long term complete remission of metastatic renal squamous cell carcinoma after palliative radiotherapy and adjuvant dichloroacetate.” Advances in Cancer: Research Treatment 2012 (2012): 441895.

pt was started on DCA 500mg orally twice a day (18mg/kg/day), on a cycle of 2 weeks on / 1 week off. Cyclic treatment was selected

due to the author’s prior experience with an unacceptable level of side effects in adult patients using continuous DCA dosing. She was prescribed benfotiamine (a lipid soluble form of vitamin B1) 80mg

orally twice a day and R-alpha lipoic acid 150mg orally 3 times a day to reduce the risk of DCA neuropathy, since both of these natural compounds have proven benefits in treating neuropathy of other etiologies (Ziegler et al. 1999), (Winkler et al. 1999). She was also started on pantoprazole 40mg orally once a day to prevent stomach upset from DCA. After the first 3 week cycle, the DCA was increased to 500mg orally three times a day (27mg/kg/day).

adds acetyl L-carnitine to the DCA neuropathy prevention regimen

DCA for RCC

10) Kinnaird, Adam, et al. “297 Dichloroacetate is a novel therapy for renal cell carcinoma.” The Journal of Urology 187.4S (2012): e120-e121.

METHODS: Two human kidney cell lines were used:

(1) A proximal tubule (PT) epithelial cell line and

(2) a clear cell RCC line that is deficient of wild type VHL tumour suppressor protein (786-0).

Cells were treated with 0.5 and 5mM DCA. Mitochondrial m and mROS

were assessed using live cell imaging with TMRM and mitosox, respec-tively. Tumor proliferation and apoptosis were measured using the

markers ki67 and TUNEL, respectively. HIF-1 activity was determined

using a firefly luciferase assay and mRNA levels quantified using

qRT-PCR. PDH activity and -ketoglutarate were measured using

commerically available kits. Angiogenesis was assessed in-vitro by

matrigel assay.

RESULTS: RCC cells have more hyperpolarized m (TMRM,

p0.001) and less mROS (Mitosox, p0.001) than PT cells. Treatment

with DCA reversed these changes in the RCC line without significantly altering PT m or mROS. This is associated with an increase in PDH activity (p0.05) and increased levels of the Krebs cycle metabolite -KG (p0.01). RCC cells are characterized by significantly more HIF-1 activity than PT cells (p0.01).

Treatment with DCA reduces mRNA levels of the HIF responsive genes GLUT1, GLUT4, and VEGF (p0.01) as well as decreasing VEGF protein level. (p0.01) RCC cells treated with DCA demonstrate decreased markers of proliferation (p0.001) and increased rates of apoptosis (p0.001).

Supernatant, containing the angiogenic signals from RCC cells was placed on microvascular endothelial cells. The supernatant from RCC cells increased vascularity (tubular structures and total length), which was blocked by DCA treatment (p0.05).

CONCLUSIONS: DCA is a novel, inexpensive, oral chemother-

apeutic agent that reverses the mitochondrial remodeling of RCC. This decreases proliferation and angiogenesis while increasing apoptosis in a human RCC line. Additional human tumor samples will be used to

generalize these findings in RCC.

Melatonin pdf

11) Reiter, Russel J., Ramaswamy Sharma, and Sergio Rosales-Corral. “Anti-Warburg effect of melatonin: a proposed mechanism to explain its inhibition of multiple diseases.” International journal of molecular sciences 22.2 (2021): 764.

Molecules, called glycolytics, inhibit aerobic glycolysis and convert cells to a healthier phenotype. Glycolytics often function by inhibiting hypoxia-inducible factor-1α leading to PDC disinhibition allowing for intramitochondrial conversion of pyruvate into acetyl coenzyme A. Melatonin is a glycolytic which converts diseased cells to the healthier phenotype. Herein we propose that melatonin’s function as a glycolytic explains its actions in inhibiting a variety of diseases. Thus, the common denominator is melatonin’s action in switching the metabolic phenotype of cells.

cancer cells, are, in fact, only of the cancer phenotype about half the time (during the day)

In healthy cells, mitochondria produce melatonin both during the day and at night, so it is always available to inhibit HIF-1α/PDK axis which allows for the upregulation of PDC and the conversion of pyruvate to acetyl-CoA, the necessary co-factor/co-substrate for melatonin synthesis (Figure 2). In contrast, in diseased cell mitochondria, melatonin synthesis does not occur because of some not yet identified metabolic change, e.g., drop in PO2, which upregulates HIF-1α, thereby shutting down mitochondrial acetyl-CoA production and melatonin formation.

Melatonin functions as a glycolytic since it also inhibits the Warburg effect.

12) Wen, Yu‐Ching, et al. “Melatonin‐triggered post‐transcriptional and post‐translational modifications of ADAMTS1 coordinately retard tumorigenesis and metastasis of renal cell carcinoma.” Journal of pineal research 69.2 (2020): e12668.

Results from protease array showed that ADAMTS1 is modulated by melatonin through mechanisms independent of the MT1 receptor in mRCC cells, and overexpression of ADAMTS1 relieved the invasion/clonogenicity and growth/metastasis inhibition imposed by melatonin treatment in vitro and in an orthotopic xenograft model.

13) Maleki Dana, Parisa, et al. “Melatonin as a potential inhibitor of kidney cancer: A survey of the molecular processes.” Iubmb Life 72.11 (2020): 2355-2365.

The studies concerned with the applications of melatonin as an adjuvant in the immunotherapy of patients with kidney cancer are summarized. Also, we highlight the apoptotic and anti-angiogenic effects of melatonin on renal cancer cells which are mediated by dif-ferent molecules (e.g., HIF-1 and VEGF, ADAMTS1, and MMP-9) and signaling

pathways (e.g., P56, P52, and JNK). Furthermore, we take a look into available data on melatonin’s ability to reduce the toxicities caused by kidney carcinogens, including ochratoxin A, potassium bromate, and Fe-NTA.

Fenbendazole

14) Ryan S Chiang Fenbendazole Enhancing Anti-Tumor Effect: A Case Series , Case Report, Clin Oncol Case Rep Vol: 4 Issue: 2

In summary, we have three patients with different primary genitourinary tumors who demonstrated complete response after receiving FBZ therapy

Case Report

A 63-year-old Caucasian male presented with flank pain, rapid weight loss, and transient fever. Abdominal Computed Topography (CT) revealed a 3 cm left lower-pole solid renal mass. He underwent open partial nephrectomy with pathology showing pT1a highgrade clear cell Renal Cell Carcinoma (RCC). Several months later, he developed persistent left flank pain with finding of a 5.2 cm left kidney mass. Fine Needle Aspiration (FNA) biopsy redemonstrated clear cell RCC, and pazopanib 800 mg was initiated. Follow-up CT revealed a new 1.4 cm pancreatic head/body lesion, persistent left renal mass, and signs of sigmoid colitis. Given the concerns for disease progression and intolerable side effects, pazopanib was discontinued and cabozantinib was initiated. Interval Magnetic Resonance Imaging (MRI) showed stable size of recurrent left renal mass, mild decrease in 2.9 cm pancreatic head lesion, stable 1.2 cm distal pancreatic body lesion, and new 1.1 cm right posterior iliac bone lesion. Cabozantinib was ultimately discontinued due to persistent intolerable side effects. One month after discontinuation, repeat MRI showed increase in size of recurrent left renal mass, mild decrease in 2.3 cm pancreatic head lesion, stable 1.4 cm distal pancreatic body lesion, and unchanged 1.1 cm right posterior iliac bone lesion. Third-line treatment with nivolumab was initiated, and he only received three total treatments (240 mg × 3) over the course of a month due to developing severe rash and colitis. He was treated with steroids with resolution of colitis.

During this time, he also started alternative therapy with FBZ 1 gm three times per week at the suggestion of one of his friends with head/neck cancer. Interval MRI imaging found near complete resolution of the previously noted left renal mass as well as decrease in pancreatic head/body and right posterior iliac spine lesions (Figure 1). Serial imaging for the past 10 months have not shown any evidence of recurrence or metastatic disease. He has continued taking FBZ without any reported side effects.

FenBen Apoptosis in Trophoblast Cells

15) Park, Hahyun, et al. “Fenbendazole induces apoptosis of porcine uterine luminal epithelial and trophoblast cells during early pregnancy.” Science of The Total Environment 681 (2019): 28-38.

Silybin Inhibits GLUT proteins

16) Zhan, Tianzuo, et al. “Silybin and dehydrosilybin decrease glucose uptake by inhibiting GLUT proteins.” Journal of cellular biochemistry 112.3 (2011): 849-859.

Silybin blocks the activity of GLUT transporter proteins

SIL against Renal Carcinoma

17) Liang L, Li L, Zeng J et al. Inhibitory effect of silibinin on EGFR signal–induced renal cell carcinoma progression via suppression of the EGFR/MMP–9 signalling pathway. Oncology Reports 2012;28:999–1005

18) Li L, Gao Y, Zhang L, Zeng J, He D, Sun Y. Silibinin inhibits cell growth and induces apoptosis by caspase activation, down regulating surviving and blocking EGFR–ERK activation in renal cell carcinoma. Cancer Lett 2008;272(1):61–69.

19) Fan, Yizeng, et al. “Silibinin inhibits epithelial‑mesenchymal transition of renal cell carcinoma through autophagy‑dependent Wnt/β‑catenin signaling.” International journal of molecular medicine 45.5 (2020): 1341-1350.

20) Ma, Zhenkun, et al. “Silibinin induces apoptosis through inhibition of the mTOR-GLI1-BCL2 pathway in renal cell carcinoma.” Oncology reports 34.5 (2015): 2461-2468.

21) Li, Feng, et al. “Autophagy induction by silibinin positively contributes to its anti-metastatic capacity via AMPK/mTOR pathway in renal cell carcinoma.” International journal of molecular sciences 16.4 (2015): 8415-8429.

22) Chang, Horng‐Rong, et al. “Silibinin inhibits the invasion and migration of renal carcinoma 786‐O cells in vitro, inhibits the growth of xenografts in vivo and enhances chemosensitivity to 5‐fluorouracil and paclitaxel.” Molecular carcinogenesis 50.10 (2011): 811-823.

Cordycepin renal cell carcinoma

23) Jang, Ik-Soon, Hyun-Jin Jang, and Eunbi Jo. “Cordycepin promotes apoptosis in renal carcinoma cells by activating the MKK7-JNK signaling pathway through inhibition of cFLIPL expression.” (2018): 4381-4381.

Specifically, cordycepin inhibited TNF-α-mediated NF-κB activation, which induced renal cancer cell apoptosis.

24) Park, Soo Jung, et al. “Cordyceps militaris extract inhibits the NF-κB pathway and induces apoptosis through MKK7-JNK signaling activation in TK-10 human renal cell carcinoma.” Natural Product Communications 13.4 (2018): 1934578X1801300422.

we found that CME dose-dependently inhibited tumor necrosis factor-α (TNF-α)-induced NF-κB activation in TK-10 human renal cell carcinoma.

CME prevented NF-κB from translocating to the nucleus, which resulted in the downregulation of GADD45B, upregulation of MKK7, and phosphorylation of JNK (p-JNK). The increased activation of Bax led to pronounced CME-induced apoptosis, which occurred through caspase-3.

Furthermore, the siRNA- mediated knockdown of GADD45B inhibited MKK7 expression, whereas the siRNA-mediated inhibition of MKK7 downregulated p-JNK and the JNK inhibitor, SP600125, inhibited Bax expression. Thus, these results indicated that CME inhibited the activation of GADD45B via the inhibition of NF-κB activation, which upregulated the MKK7-JNK signaling pathway to induce apoptosis in TK-10 cells.

25) Hwang, In-Hu, et al. “Cordycepin promotes apoptosis in renal carcinoma cells by activating the MKK7-JNK signaling pathway through inhibition of c-FLIPL expression.” PLoS One 12.10 (2017): e0186489.

Taken together, the results indicate that cordycepin inhibits TNF-α-mediated NF-κB/GADD45B signaling, which activates the MKK7-JNK signaling pathway through inhibition of c-FLIPL expression, thus inducing TK-10 cell apoptosis.

26) Yang, Chao, et al. “Cordycepin induces apoptotic cell death and inhibits cell migration in renal cell carcinoma via regulation of microRNA-21 and PTEN phosphatase.” Biomedical Research 38.5 (2017): 313-320.

27) Hwang, Jung-Hoo, et al. “Cordycepin promotes apoptosis by modulating the ERK-JNK signaling pathway via DUSP5 in renal cancer cells.” American journal of cancer research 6.8 (2016): 1758.

28) Özenver, Nadire, Joelle C. Boulos, and Thomas Efferth. “Activity of Cordycepin From Cordyceps sinensis Against Drug-Resistant Tumor Cells as Determined by Gene Expression and Drug Sensitivity Profiling.” Natural Product Communications 16.2 (2021): 1934578X21993350.

The drug sensitivity profiles of several DNA Topo I and II inhibitors were significantly correlated with those of cordycepin’s activity. Among eight different tumor types, prostate cancer was the most sensitive, whereas renal carcinoma was the most resistant to cordycepin.

Cordycepin exerted an anticancer function through stimulating the adenosine A3 receptor followed by GSK-3β activation and cyclin D1 repression.

Furthermore, cordycepin displayed an antimetastatic property through inhibiting platelet aggregation initiated by ADP liberated from cancer cells and easing invasiveness of cancer cells via suppressing matrix metalloproteinase (MMP-2, MMP-9) activities, as well as enhancing tissue inhibitor of matrix metalloproteinase (TIMP-1, TIMP-2) secretions from those cells.

Cordycepin exerts anti-inflammatory activity

29) Yoon, So Young, Soo Jung Park, and Yoon Jung Park. “The anticancer properties of cordycepin and their underlying mechanisms.” International journal of molecular sciences 19.10 (2018): 3027.

30) Jin, Ye, et al. “Anti-tumor and anti-metastatic roles of cordycepin, one bioactive compound of Cordyceps militaris.” Saudi journal of biological sciences 25.5 (2018): 991-995.

Cordyceps Renal Protection

31) Wang, Ying, et al. “Protection of chronic renal failure by a polysaccharide from Cordyceps sinensis.” Fitoterapia 81.5 (2010): 397-402.

32) Chiu, Chun-Hung, et al. “Polysaccharide extract of Cordyceps sobolifera attenuates renal injury in endotoxemic rats.” Food and Chemical Toxicology 69 (2014): 281-288.

33) Chyau, Charny-Cherng, et al. “Mycelia glycoproteins from Cordyceps sobolifera ameliorate cyclosporine-induced renal tubule dysfunction in rats.” Journal of ethnopharmacology 153.3 (2014): 650-658.

Thymoquinone for RCC

34) Chae, In Gyeong, et al. “Thymoquinone induces apoptosis of human renal carcinoma Caki-1 cells by inhibiting JAK2/STAT3 through pro-oxidant effect.” Food and Chemical Toxicology 139 (2020): 111253.

However, treatment with the ROS scavenger N-acetyl cysteine significantly blocked TQ-induced apoptosis as well as incorporated signaling pathways, supporting that its pro-oxidant property is crucial for Caki-1 cell apoptosis. Moreover, TQ reduced the tumor xenograft growth of Caki-1 cells in nude mice. Taken together, these data suggest that TQ is a prominent anti-cancer drug to treat human RCC by enhancing apoptosis through its pro-oxidant nature.

35) Lee, Yoon-Mi, et al. “Thymoquinone selectively kills hypoxic renal cancer cells by suppressing HIF-1α-mediated glycolysis.” International journal of molecular sciences 20.5 (2019): 1092.

The major findings of this study are that

1) thymoquinone (TQ) was identified as an HIF-1α inhibitor using a 502 natural compound library,

2) TQ suppressed hypoxia-induced HIF-1α by suppressing HSP90-mediated stabilization and target genes’ expression,

3) TQ alters hypoxic anaerobic glycolysis and causes metabolic stress, and

4) TQ selectively killed hypoxic renal cancer cells. Overall, our finding suggested that TQ, as an HIF-1α inhibitor, is a potential natural compound involved in clearance of hypoxic renal cancer cells.

Dr. Lee’s group then studied the anti-cancer effects of TQ on a renal cell cancer line, writing that TQ rapidly degrades HIF-1 protein and

kills hypoxic renal cancer cells:

TQ causes rapid degradation of HIF-1α by inhibiting interaction between HIF-1α and HSP90 … TQ suppressed HIF-1α protein levels,

which significantly downregulated the hypoxia-induced tumor-promoting HIF-1α target genes … TQ Suppresses Glycolysis [the Warburg Effect] in Hypoxic Renal Cancer Cells, … TQ-mediated suppression of angiogenesis via HIF-mediated VEGF expression. (22)

Accumulation of Autophagosomes Thymoquinone TQ

Similar upregulation of autophagy with accumulation of autophagosomes was seen in 2018 by Dr. Yujiao Zhang et al. in a renal cell

cancer model treated with TQ. In this model, inhibition of autophagy with 3‐methyladenine (3‐MA) attenuated the anti-cancer effects of

TQ.

Treatment with TQ caused AMPK activation and downregulated mTOR, which stimulated autophagy. TQ significantly inhibited renal cell

cancer growth and metastasis in an in vivo mouse xenograft model, via inhibition of EMT (epithelial to mesenchymal transition). In this

model, TQ stimulated early stage autophagy. However, late-stage autophagy was blocked, as indicated by accumulation of autophagosomes with good inhibition of metastasis. (24)

36) Zhang, Yujiao, et al. “Thymoquinone inhibits the metastasis of renal cell cancer cells by inducing autophagy via AMPK/mTOR signaling pathway.” Cancer science 109.12 (2018): 3865-3873

Thymoquinone Renal Protective

37) Al Fayi, Majed, et al. “Thymoquinone and curcumin combination protects cisplatin-induced kidney injury, nephrotoxicity by attenuating NFκB, KIM-1 and ameliorating Nrf2/HO-1 signalling.” Journal of drug targeting 28.9 (2020): 913-922.

38) Abdel-Daim, Mohamed M., et al. “Thymoquinone and diallyl sulfide protect against fipronil-induced oxidative injury in rats.” Environmental Science and Pollution Research 25.24 (2018): 23909-23916.

39) Ragheb, Ahmed, et al. “The protective effect of thymoquinone, an anti-oxidant and anti-inflammatory agent, against renal injury: a review.” Saudi Journal of Kidney Diseases and Transplantation 20.5 (2009): 741.

Pterostilbene for RCC

40) Zhao, Yuwan, et al. “Pterostilbene inhibits human renal cell carcinoma cells growth and induces DNA damage.” Biological and Pharmaceutical Bulletin 43.2 (2020): 258-265.

Pterostilbene Renoprotective

41) Gao, Dan, et al. “Pterostilbene protects against acute renal ischemia reperfusion injury and inhibits oxidative stress, inducible nitric oxide synthase expression and inflammation in rats via the Toll‑like receptor 4/nuclear factor‑κB signaling pathway.” Experimental and therapeutic medicine 15.1 (2018): 1029-1035.

42) Xia, Yizi, et al. “Pterostilbene attenuates acute kidney injury in septic mice.” Experimental and therapeutic medicine 15.4 (2018): 3551-3555.

PET SCAN for RCC

43) Ferda, Jiri, et al. “18F-FDG-PET/CT in potentially advanced renal cell carcinoma: a role in treatment decisions and prognosis estimation.” Anticancer research 33.6 (2013): 2665-2672.

44) Courtney, Kevin D., et al. “Isotope tracing of human clear cell renal cell carcinomas demonstrates suppressed glucose oxidation in vivo.” Cell metabolism 28.5 (2018): 793-800.

45) Keshari, Kayvan R., et al. “Hyperpolarized 13C-pyruvate magnetic resonance reveals rapid lactate export in metastatic renal cell carcinomas.” Cancer research 73.2 (2013): 529-538.

GLUTAMINE Addiction RCC

46) Hoerner, Christian R., Viola J. Chen, and Alice C. Fan. “The ‘Achilles Heel’of metabolism in renal cell carcinoma: glutaminase inhibition as a rational treatment strategy.” Kidney Cancer 3.1 (2019): 15-29.

47) Novel inhibitors of glutaminase, a key enzyme in glutamine metabolism, target glutamine addiction as a viable treatment strategy in metastatic RCC (mRCC).

48) Aboud, Omran Abu, et al. “Glutamine addiction in kidney cancer suppresses oxidative stress and can be exploited for real-time imaging.” Cancer research 77.23 (2017): 6746-6758.

49) Sanchez, Danielle J., and M. Celeste Simon. “Genetic and metabolic hallmarks of clear cell renal cell carcinoma.” Biochimica et Biophysica Acta (BBA)-Reviews on Cancer 1870.1 (2018): 23-31.

Since being reviewed by Wettersten, et al. [3], two phase II clinical trials have been initiated to examine the effect of CB-839, a small molecule inhibitor of glutaminase, along with either cabozantinib, everolimus, or placebo, on patients with advanced or metastatic RCC [105]. Additionally, a pre-clinical report on the role of glutamine addiction in ccRCC further supports the possibility of therapeutically targeting this axis in kidney cancer [106]. Aboud, et al. demonstrate that ccRCC tumors grown orthotopically show increased uptake of 18F-(2S,4R)4-fluoroglutamine relative to adjacent healthy kidney tissue and are sensitive to glutaminase inhibition by CB-839. These results suggest that PET imaging could be useful to identify ccRCC patients likely to respond to glutaminase inhibition clinically.

50) Hoerner, Christian R., Viola J. Chen, and Alice C. Fan. “The ‘Achilles Heel’of metabolism in renal cell carcinoma: glutaminase inhibition as a rational treatment strategy.” Kidney Cancer 3.1 (2019): 15-29.

Novel inhibitors of glutaminase, a key enzyme in glutamine metabolism, target glutamine addiction as a viable treatment strategy in metastatic RCC (mRCC).

51) Altman, Brian J., Zachary E. Stine, and Chi V. Dang. “From Krebs to clinic: glutamine metabolism to cancer therapy.” Nature Reviews Cancer 16.10 (2016): 619-634.

OxaloAcetate

52) Kuang, Ye, et al. “Oxaloacetate induces apoptosis in HepG2 cells via inhibition of glycolysis.” Cancer medicine 7.4 (2018): 1416-1429.

we confirmed the anticancer effect of OA in vivo and in vitro. We found that the OA- mediated apoptosis in cancer cells was related to the inhibition of aerobic glycolysis. We further found that OA inhibited

glycolysis via enhancement of OXPHOS and suppression of the Akt/HIF pathway. In addition, our preliminary study revealed that OA selectively inhibited cancer cells with high levels of glycolysis.

Platelets

53) Wang, Jun, et al. “The platelet isoform of phosphofructokinase contributes to metabolic reprogramming and maintains cell proliferation in clear cell renal cell carcinoma.” Oncotarget 7.19 (2016): 27142.

Erythropoetin Stimulates Proliferation

54) Erythropoietin stimulates proliferation of human renal carcinoma cells Christof Westenfelder Robert L.Baranowski

55) Bachman, Eric, et al. “Testosterone induces erythrocytosis via increased erythropoietin and suppressed hepcidin: evidence for a new erythropoietin/hemoglobin set point.” Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences 69.6 (2014): 725-735.

RCC is Highly Glycolytic

56) Zhang, Yan, et al. “Glycolysis-related genes serve as potential prognostic biomarkers in clear cell renal cell carcinoma.” Oxidative Medicine and Cellular Longevity 2021 (2021).

We used bioinformatics to explore glycolytic genes that are differentially expressed in 539 ccRCC tissues and 72 normal control tissues from The Cancer Genome Atlas (TCGA). A predictive model containing 13 genes was established after performing a series of investigations, including pathway analysis, drug sensitivity analysis, gene coexpression analysis, Lasso regression analysis, and survival curve analysis. This model showed great promise for the diagnosis and prognosis of ccRCC and may help in the identification of potential prognostic biomarkers and drug targets in ccRCC.

57) Lv, Zhengtong, et al. “Identification of a Novel Glycolysis-Related Gene Signature Correlates With the Prognosis and Therapeutic Responses in Patients With Clear Cell Renal Cell Carcinoma.” Frontiers in oncology 11 (2021): 482.

58) Ambrosetti, Damien, et al. “The two glycolytic markers GLUT1 and MCT1 correlate with tumor grade and survival in clear-cell renal cell carcinoma.” PloS one 13.2 (2018): e0193477.

59) Sudarshan, Sunil, et al. “Fumarate hydratase deficiency in renal cancer induces glycolytic addiction and hypoxia-inducible transcription factor 1α stabilization by glucose-dependent generation of reactive oxygen species.” Molecular and cellular biology 29.15 (2009): 4080-4090.

60) Zhang, Chuanjie, et al. “Downregulated METTL14 accumulates BPTF that reinforces super-enhancers and distal lung metastasis via glycolytic reprogramming in renal cell carcinoma.” Theranostics 11.8 (2021): 3676.

61) Zhang, Huafeng, et al. “HIF-1 inhibits mitochondrial biogenesis and cellular respiration in VHL-deficient renal cell carcinoma by repression of C-MYC activity.” Cancer cell 11.5 (2007): 407-420.

62) Zheng, Jinzhou, et al. “Traditional Chinese medicine Bu-Shen-Jian-Pi-Fang attenuates glycolysis and immune escape in clear cell renal cell carcinoma: results based on network pharmacology.” Bioscience Reports 41.6 (2021): BSR20204421.

63) Chan, Denise A., et al. “Targeting GLUT1 and the Warburg effect in renal cell carcinoma by chemical synthetic lethality.” Science translational medicine 3.94 (2011): 94ra70-94ra70.

To discover compounds that selectively target RCC, we screened ~64,000 small molecules to identify those that functioned in a synthetic lethal manner to the loss of VHL.

These data suggest that renal cells with defective VHL, like a range of other cancers, are highly dependent on aerobic glycolysis for energy production

GLUT1 levels were high in renal carcinomas, whereas GLUT2 levels were high in normal renal cells

64) Gerlinger, Marco, et al. “Genome‐wide RNA interference analysis of renal carcinoma survival regulators identifies MCT4 as a Warburg effect metabolic target.” The Journal of pathology 227.2 (2012): 146-156.

65) Xing, Qianwei, et al. “A novel 10 glycolysis-related genes signature could predict overall survival for clear cell renal cell carcinoma.” BMC cancer 21.1 (2021): 1-15.

66) Guo, Yuanyuan, et al. “Oncogenic Chromatin Modifier KAT2A Activates MCT1 to Drive the Glycolytic Process and Tumor Progression in Renal Cell Carcinoma.” Frontiers in Cell and Developmental Biology 9 (2021).

Prognostic analysis indicated that a high KAT2A was an independent biomarker and associated with poor survival outcomes. KAT2A could promote RCC proliferation and distal metastasis in vitro and in vivo. Transcriptome analysis and ChIP-seq were combined to find that KAT2A mainly regulated the glycolytic process. Validation and rescue assays revealed that MCT1 was the downstream target of KAT2A, and KAT2A depended on MCT1 to promote RCC malignant phenotypes. Lastly, MCT1 inhibitor (AZD3965) was effective to treat KAT2A-induced RCC progression.

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DCA and Quercetin

67) Xintaropoulou, Chrysi, et al. “A comparative analysis of inhibitors of the glycolysis pathway in breast and ovarian cancer cell line models.” Oncotarget 6.28 (2015): 25677.

Quercetin

68) Han, C. G. H., and W. Zhang. “The anti-cancer effect of Quercetin in renal cancer through regulating survivin expression and caspase 3 activity.” Med. One 1.7 (2016).

69) Quercetin is known to be a MCT inhibitor

Vasodilatory action: “During the injection of quercetin, all of the patients experienced transient flushing for up to S mm. This was not associated with a fall in blood pressure, and must therefore be related to dilation of blood vessels smaller than resistance vessels.

Fenofibrate – Impair Renal function

Fenofibrate fenofibrate, a peroxisome proliferator-activated receptor (PPAR)-alpha agonist,

70) Paul, S., and V. Mohan. “Fenofibrate can increase serum creatinine levels in renal insufficiency.” The Journal of the Association of Physicians of India 54 (2006): 337.

71) Abu Aboud, Omran, Hiromi I. Wettersten, and Robert H. Weiss. “Inhibition of PPARα induces cell cycle arrest and apoptosis, and synergizes with glycolysis inhibition in kidney cancer cells.” PloS one 8.8 (2013): e71115.

72) Ananth, Subbian, et al. “Transforming growth factor β1 is a target for the von Hippel-Lindau tumor suppressor and a critical growth factor for clear cell renal carcinoma.” Cancer research 59.9 (1999): 2210-2216.

73) YANG, Feng‐guang, et al. “Peroxisome proliferator‐activated receptor γ ligands induce cell cycle arrest and apoptosis in human renal carcinoma cell lines 1.” Acta Pharmacologica Sinica 26.6 (2005): 753-761.

74) Chu, Quincy Siu-Chung, et al. “A phase I open-labeled, single-arm, dose-escalation, study of dichloroacetate (DCA) in patients with advanced solid tumors.” Investigational new drugs 33.3 (2015): 603-610.

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Diclofenac Impairs renal Function

75) Gerlinger, Marco, et al. “Genome‐wide RNA interference analysis of renal carcinoma survival regulators identifies MCT4 as a Warburg effect metabolic target.” The Journal of pathology 227.2 (2012): 146-156.

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76) ung, Joo Eun, et al. “Caffeic acid and its synthetic derivative CADPE suppress tumor angiogenesis by blocking STAT3-mediated VEGF expression in human renal carcinoma cells.” Carcinogenesis 28.8 (2007): 1780-1787.

EGF Epidermal growth factor (EGF) Upregulated

77) Price, J. T., H. M. Wilson, and N. E. Haites. “Epidermal growth factor (EGF) increases the in vitro invasion, motility and adhesion interactions of the primary renal carcinoma cell line, A704.” European Journal of Cancer 32.11 (1996): 1977-1982.

78) Morris, Zachary S., and Andrea I. McClatchey. “Aberrant epithelial morphology and persistent epidermal growth factor receptor signaling in a mouse model of renal carcinoma.” Proceedings of the National Academy of Sciences 106.24 (2009): 9767-9772.

78a) Zhang, Hong, et al. “Lectin PCL inhibits the Warburg effect of PC3 cells by combining with EGFR and inhibiting HK2.” Oncology reports 37.3 (2017): 1765-1771.

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PET Imaging

79) Vercellino, Laetitia, et al. “18F-FDG PET/CT imaging for an early assessment of response to sunitinib in metastatic renal carcinoma: preliminary study.” Cancer biotherapy & radiopharmaceuticals 24.1 (2009): 137-144.

Curcumin

80) Xu, Shan, et al. “Curcumin enhances temsirolimus-induced apoptosis in human renal carcinoma cells through upregulation of YAP/p53.” Oncology Letters 12.6 (2016): 4999-5006.

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Allicin Suppresses HIF

81) Song, Bin, et al. “Allicin inhibits human renal clear cell carcinoma progression via suppressing HIF pathway.” International journal of clinical and experimental medicine 8.11 (2015): 20573.

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82) Nilsson, Helén, et al. “Primary clear cell renal carcinoma cells display minimal mitochondrial respiratory capacity resulting in pronounced sensitivity to glycolytic inhibition by 3-Bromopyruvate.” Cell death & disease 6.1 (2015): e1585-e1585.

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Even though many tumor types display a high degree of aerobic glycolysis, they still retain the activity of other energy-producing metabolic pathways. One exception seems to be the clear cell variant of renal cell carcinoma, ccRCC, where the activity of most other pathways than that of glycolysis has been shown to be reduced. This makes ccRCC a promising candidate for the use of glycolytic inhibitors in treatment of the disease. However, few studies have so far addressed this issue. In this report, we show a strikingly reduced mitochondrial respiratory capacity of primary human ccRCC cells, resulting in enhanced sensitivity to glycolytic inhibition by 3-Bromopyruvate (3BrPA). This effect was largely absent in established ccRCC cell lines, a finding that highlights the importance of using biologically relevant models in the search for new candidate cancer therapies. 3BrPA markedly reduced ATP production in primary ccRCC cells, followed by cell death. Our data suggest that glycolytic inhibitors such as 3BrPA, that has been shown to be well tolerated in vivo, should be further analyzed for the possible development of selective treatment strategies for patients with ccRCC.

Cimetidine

cimetidine 800 mg orally

83) [Successful treatment of metastatic renal cell carcinoma with cimetidine–report of two cases] [Article in Japanese] T Nagano 1 , H Matsuda, Y C Park, T Kurita

There has been no effective therapy for metastatic renal cell carcinoma (RCC). Cimetidine has been demonstrated to block histamine mediated activation of suppressor T cells in man and in animal models, resulting in an anti-tumor immune response. We treated two patients with cimetidine for matastatic RCC. Case 1: A 61-year-old man presented with a diagnosis of metastatic lung and brain tumor of RCC. Interferon therapy was not effective, but after radiation therapy, his brain metastasis revealed partial response. He received cimetidine 800 mg orally after radiation, his lung metastasis revealed almost complete response. But he died of ischemic heart disease. Case 2: A 58-year-old woman presented with a metastatic lung tumor of RCC. We started interferon therapy. But because of general fatigue and anemia, she required discontinution of interferon therapy. So she received cimetidine 800 mg orally and her lung metastasis revealed complete response. She remained well and had no evidence of disease. Patients with metastatic renal cell carcinoma can occasionally respond to cimetidine and further investigation must be studied.

Cimetidine

84) Inhorn, L., et al. “High-dose cimetidine for the treatment

of metastatic renal cell carcinoma. A Hoosier Oncology Group study.” American journal of clinical oncology 15.2 (1992): 157-159.

The Hoosier Oncology Group evaluated cimetidine in 42 patients with metastatic renal cell carcinoma. There were two complete remissions that lasted for 26 and 33+ months in 38 evaluable patients. There were no partial remissions. Toxicity was minimal. Patients with renal cell carcinoma can occasionally respond to cimetidine with long-term remission.

Atovaquone

85) Chen, Dehong, et al. “Targeting mitochondria by anthelmintic drug atovaquone sensitizes renal cell carcinoma to chemotherapy and immunotherapy.” Journal of biochemical and molecular toxicology 32.9 (2018): e22195.

86) Fiorillo, Marco, et al. “Repurposing atovaquone: targeting mitochondrial complex III and OXPHOS to eradicate cancer stem cells.” Oncotarget 7.23 (2016): 34084.

87) Stevens, Alexandra M., et al. “Atovaquone is active against AML by upregulating the integrated stress pathway and suppressing oxidative phosphorylation.” Blood advances 3.24 (2019): 4215-4227.

88) Guo, Yue, et al. “Atovaquone at clinically relevant concentration overcomes chemoresistance in ovarian cancer via inhibiting mitochondrial respiration.” Pathology-Research and Practice (2021): 153529.

89) Xie, Fan, et al. “Preclinical evidence of synergism between atovaquone and chemotherapy by AMPK-dependent mitochondrial dysfunction.” European Journal of Pharmacology (2021): 174256.

Sulforaphane for renal cell carcinoma

90) Juengel, Eva, et al. “Sulforaphane inhibits proliferation and invasive activity of everolimus-resistant kidney cancer cells in vitro.” Oncotarget 7.51 (2016): 85208.

91) Juengel, Eva, et al. “Relevance of the natural HDAC inhibitor sulforaphane as a chemopreventive agent in urologic tumors.” Cancer letters 435 (2018): 121-126.

92) Juengel, Eva, et al. “Sulforaphane as an adjunctive to everolimus counteracts everolimus resistance in renal cancer cell lines.” Phytomedicine 27 (2017): 1-7

93) Naujokat, Cord, and Dwight L. McKee. “The “Big Five” phytochemicals targeting cancer stem cells: curcumin, EGCG, sulforaphane, resveratrol, and genistein.” Current medicinal chemistry (2021).

Sulforaphane Renoprotective

94) Negrette-Guzmán, Mario, et al. “Sulforaphane attenuates gentamicin-induced nephrotoxicity: role of mitochondrial protection.” Evidence-Based Complementary and Alternative Medicine 2013 (2013).

95) Yoon, Ha-Yong, et al. “Sulforaphane protects kidneys against ischemia-reperfusion injury through induction of the Nrf2-dependent phase 2 enzyme.” Biochemical pharmacology 75.11 (2008): 2214-2223.

96) Guerrero-Beltrán, Carlos Enrique, et al. “Sulforaphane, a natural constituent of broccoli, prevents cell death and inflammation in nephropathy.” The Journal of nutritional biochemistry 23.5 (2012): 494-500.

Quercetin RCC

97) Meng, Fan-Dong, et al. “Synergistic effects of snail and quercetin on renal cell carcinoma Caki-2 by altering AKT/mTOR/ERK1/2 signaling pathways.” International journal of clinical and experimental pathology 8.6 (2015): 6157.

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Artesunate

98) Da Eun Jeong, Hye Jin Song, et al. Repurposing the anti-malarial drug artesunate as a novel therapeutic agent for metastatic renal cell carcinoma due to its attenuation of tumor growth, metastasis, and angiogenesis.” Oncotarget 6.32 (2015): 33046.

Niclosamide

99) Zhao, Juan, et al. “Niclosamide suppresses renal cell carcinoma by inhibiting Wnt/β-catenin and inducing mitochondrial dysfunctions.” SpringerPlus 5.1 (2016): 1436.

100) Yu, Xinyi, et al. “Niclosamide exhibits potent anticancer activity and synergizes with sorafenib in human renal cell cancer cells.” Cellular Physiology and Biochemistry 47.3 (2018): 957-971.

Mifepristone

101) Check, Jerome H., et al. “Long-term high-quality survival with single-agent mifepristone treatment despite advanced cancer.” Anticancer research 36.12 (2016): 6511-6513.

In 2016, Dr. Check et al. reported on two advanced cancer patients who dramatically improved their long-term survival on mifepristone.

The second patient, a male, had bilateral renal carcinoma treated with heminephrectomy (only part of one kidney was surgically

removed, with cancer remaining behind) and survived 12 years on the drug. There were no adverse effects from the drug for either patient. (23)

Pyrvinium for RCC

102) Cui, Long, Juan Zhao, and Jingjing Liu. “Pyrvinium sensitizes clear cell renal cell carcinoma response to chemotherapy via casein kinase 1α-dependent inhibition of Wnt/β-catenin.” The American journal of the medical sciences 355.3 (2018): 274-280.

**Green Tea**

103) Carvalho, Márcia, et al. “Green tea: A promising anticancer agent for renal cell carcinoma.” Food Chemistry 122.1 (2010): 49-54.

104) Chen, Shao‑Jun, et al. “Epigallocatechin-3-gallate inhibits migration and invasion of human renal carcinoma cells by downregulating matrix metalloproteinase-2 and matrix metalloproteinase-9.” Experimental and therapeutic medicine 11.4 (2016): 1243-1248.

105) Gu, Bin, et al. “EGCG inhibits growth and induces apoptosis in renal cell carcinoma through TFPI-2 overexpression.” Oncology reports 21.3 (2009): 635-640.

106) Johnson, Derek, et al. “Abstract# 5079: Functional and genomic response of human renal cell cancer (RCC) to epigallocatechin 3-gallate (EGCG).” (2009): 5079-5079.

107) Braun, D. P., et al. “Apoptotic and immunomodulatory effects of green tea extracts (GTE) on chemoresistant human tumor cells.” Journal of Clinical Oncology 27.15\_suppl (2009): e22101-e22101.

Hedgehog pathway

108) Dormoy, Valérian, et al. “The sonic hedgehog signaling pathway is reactivated in human renal cell carcinoma and plays orchestral role in tumor growth.” Molecular cancer 8.1 (2009): 1-16.

109) D’Amato, C., et al. “Inhibition of Hedgehog signalling by NVP-LDE225 (Erismodegib) interferes with growth and invasion of human renal cell carcinoma cells.” British journal of cancer 111.6 (2014): 1168-1179.

Vitamin D3 – Hedgehog Pathway

110) Dormoy, Valérian, et al. “Vitamin D3 triggers antitumor activity through targeting hedgehog signaling in human renal cell carcinoma.” Carcinogenesis 33.11 (2012): 2084-2093.

Itraconazole Hedgehog

111) Wei, Xin, et al. ““Hedgehog pathway”: a potential target of itraconazole in the treatment of cancer.” Journal of cancer research and clinical oncology 146.2 (2020): 297-304.

Resveratrol Hedgehog

112) Sun, Hongliang, et al. “Resveratrol inhibition of renal cancer stem cell characteristics and modulation of the sonic hedgehog pathway.” Nutrition and cancer 73.7 (2021): 1157-1167.

ATP Citrate Lysase

113) Teng, Lichen, et al. “Overexpression of ATP citrate lyase in renal cell carcinoma tissues and its effect on the human renal carcinoma cells in vitro.” Oncology letters 15.5 (2018): 6967-6974.

HCQ – Autophagy

114) Lee, Hyung-Ok, et al. “Hydroxychloroquine destabilizes phospho-S6 in human renal carcinoma cells.” PLoS One 10.7 (2015): e0131464.

115) Mao, Ruizhe, et al. “Hydroxychloroquine Potentiates Apoptosis Induced by PPARα Antagonist in 786-O Clear Cell Renal Cell Carcinoma Cells Associated with Inhibiting Autophagy.” PPAR research 2021 (2021).

116) Jones, Trace M., Jennifer S. Carew, and Steffan T. Nawrocki. “Therapeutic targeting of autophagy for renal cell carcinoma therapy.” Cancers 12.5 (2020): 1185.

HCQ in combination with vorinostat, an FDA approved histone deacetylase (HDAC) inhibitor [54]. This trial included patients with a variety of advanced solid tumors who had failed conventional

therapy. Of these patients, a single person presented with advanced RCC. This particular patient had failed seven previous lines of therapy. A durable, partial response was obtained with a regimen of 400 mg vorinostat and 400 mg HCQ, administered daily. This response was maintained for more than 50 three-week cycles of the drug combination. This remarkable result in an RCC patient has sparked follow-up studies to evaluate tumor characteristics that may be indicative of a positive response to concurrent HDAC and autophagy inhibition.

117) Fatty acid synthase over expression is an indicator of tumor aggressiveness and poor prognosis in renal cell carcinoma

Akio Horiguchi

118) Stearoyl-CoA Desaturase 1 Is a Novel Molecular Therapeutic Target for Clear Cell Renal Cell Carcinoma Christina A. von Roemeling, Laura A. Marlow, Johnny J. Wei, Simon J. Cooper, Thomas R. Caulfield, Kevin Wu, Winston W. Tan, Han W. Tun and John A. Copland Published May 2013