International Journal of Innovation Scientific Research and Review
Vol. 05, Issue, 01, pp.3813-3817, January 2023
Available online at http://www.journalijisr.com
SJIF Impact Factor 4.95

IJISRR

ISSN: 2582-6131

Research Article

THE TREATMENT OF CANCER WITH LITHIUM

*** Malcolm Traill, MBBS**

Clinical Pathologist (Retired), Castlemaine, Victoria, Australia.

Received 15th November 2022; Accepted 16th December 2022; Published online 22th January 2023

ABSTRACT

Lithium, when administered in an alternate day protocol, causes cancer cell Necroptosis. This can be detected and monitored by spot urine Calcium concentration tests. The Lithium action appears to inhibit production &/or maintenance of Glucose transporter(s), causing Glucose starvation. For some patients, treatment may be indefinite.

Conclusion: Alternate day Lithium dosing to cancer patients may cause Necroptosis and cell death by inducing a block in cellular glucose uptake.

Index terms: Cancer, Lithium, Necroptosis, Glucose transporter.

INTRODUCTION

Janković *et al.,* (1979-1982) and his group (1984) published a series of experiment results involving inflammatory conditions in animals. They noted that, when the Lithium was administered every day, the animals developed the marker condition but, when administered every second day, the condition was prevented, (or reduced in severity). This strange effect was confirmed by Levine & Saltzman with experimental allergic encephalomyelitis. But the mechanism remained unknown. In 2008, a man with clinically probable prostate cancer was prepared to try alternate-day Lithium. His PSA was ~12, and he was 68. Plans were initiated for a biopsy. He was told to take Lithium carbonate tablets, 1g on alternate days, (based upon the animal experiments by Janković *et al.*,) and trans-rectal core biopsies followed in 3 weeks.

These showed reasonably typical moderately differentiated adenocarcinoma of the prostate (Figure 1); so there was a radical prostatectomy on day 83 from starting the Lithium doses. The Histopathology report confirmed adenocarcinoma of the prostate, with extension to the excision line and peri-neural spread. Post-operative PSAs# were positive; the likelihood of recurrence was very high.

#Serum Prostate Specific Antigen tests

The histopathology sections were reviewed (Figures 2 & 3). The prostate had patchy degenerative changes characterized by the loss of the gland lumens - with degenerating cells showing pyknotic nuclei (i.e. shrunken and dark) piled-up in the glands' stromal tubes with, seemingly, minimal cell-to-cell cohesion or attachment to the basement membrane (the wall). (See Figures 2 & 3). The appearances seemed quite unusual:

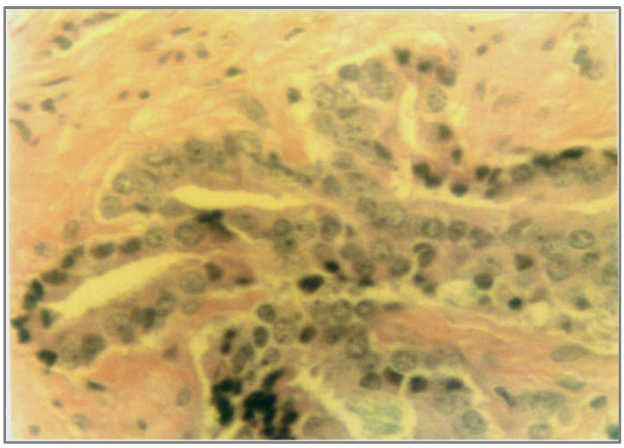


Figure 1: Photomicrograph of the core biopsy (treatment day 21) histopathology, high power, showing a typical adenocarcinoma gland structure, but with occasional pyknotic nuclei at the depths of the glands. (High power, H&E.)

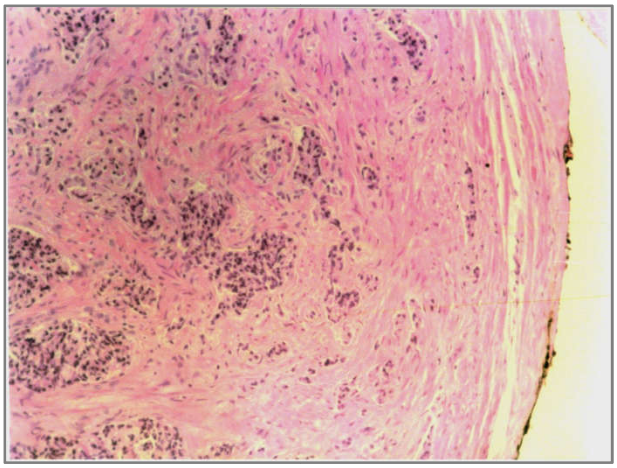


Figure 2: Low power photomicrograph of a section through the prostatectomy specimen. Typical gland structures are largely absent. What remain are the stromal tubes filled with the detached epithelial cells separated from the basement membranes and themselves, and have piled-up in the tubes, with pyknotic nuclei now prominent. The absence of any gland lumen is a noticeable feature. (Low power H&E.)

***Corresponding Author: Malcolm Traill, MBBS,**
Clinical Pathologist (Retired), Castlemaine, Victoria, Australia.
matraill@iprimus.com.au

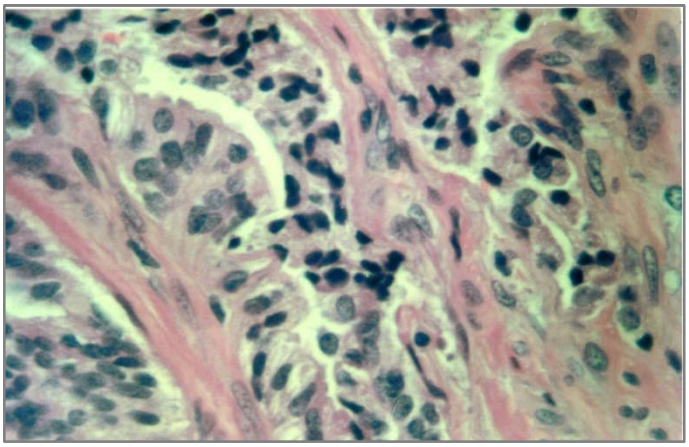


Figure 3: High power photomicrograph of the adenocarcinoma of the prostate. The man had 83 days of alternate-day Lithium carbonate 1 g/treatment day (see Janković and Levine & Saltzman).The view is taken from a transition zone. Between fibro-muscular bands (pink), are glandular cells. Those about 1/3 from the left are more typical columnar cancer glandular cells. To their upper right there is a band of disorganized, cells with very pyknotic nuclei (with a sudden transition at the lower end), and another band further to the right. The pyknotic cells show poor cell-to-cell adhesion and a loss of adhesion to the connective tissue, with wispy cytoplasm. Nuclear fragmentation (a feature of apoptosis) is not a feature and there are few (if any) inflammatory cells.

Review of the core biopsies showed minimal changes (in retrospect); perhaps some patchy, and mild pyknosis (Figure 1). Accordingly, as an estimate, the degeneration probably started about 2 months into the Lithium treatment (there was no other form of treatment or medication which might have had hormonal activity). The nature of the degeneration was not clear, and further consideration was deferred until biochemical tests on urine became available (see later). This case may be a world first. Later, the conclusion was that the degeneration was due to Necroptosis (Gong *et al.,* 2017, Samson, 2020), a form of programmed "*cytoplasmic cell death,*" occurring when apoptosis ("*nuclear cell death*") is unable to proceed because of energy/ATP deficiency. A key step is plasma membrane damage by the enzyme MLKL (Gong *et al.,* 2017) making the membrane porous.

(The man is still taking alternate-day Lithium without any sign or symptom attributable to the cancer, and no sign or symptom attributable to the long-term Lithium use [other than a slightly under-active thyroid – treated.])

Treatments* of incurable cancer patients during 2017-2020 involved hyperthermia, administered by a Chinese NRL-003 unit at radio-frequencies 26-40 MHz for 1 h. This could raise core temperatures to ~41°C and was delivered to regions by capacitative induction. Lithium was introduced with the belief that, if tablets of Lithium carbonate were consumed by the patients on the day before (1 g) and on the morning of the hyperthermia (0.5 g) the production of Tumour Necrosis Factor-alpha (TNF) (Kleinerman *et al.,* 1989) and other Death Ligands, could boost the effects of the hyperthermia.

*All approved by the Ethics Committee.

To study and monitor the effects, (initially) daily spot urine specimens were tested manually for concentrations of Phosphate (indicating apoptosis; Molybdate method, P), Uric Acid (indicating apoptosis; Uricase/UV method, U) and Calcium (o-Cresolphthalein complexone method, because it was cheap and easy to perform; Ca^{++}), with all results expressed in relation to the relevant days' Creatinine (C) concentrations. (Results are arbitrary, individual units.). Spot urine specimens were generally collected by the patients about midday and kept cool/refrigerated until delivered; the pH was adjusted to ~7 and they were then frozen.

Treatments centred around the hyperthermia sessions, which were recommended every 2nd or 3rd day, but sometimes longer intervals, accommodating patients' wishes, so that the Lithium treatments initially matched this arrangement, with no consecutive daily treatment sequences. At the patients' convenience, gaps were often longer, especially if their interest flagged.

The results with this protocol did not seem very good, so patients were advised to take the Lithium on an alternate day basis and have the hyperthermia at their convenience. Results then seemed better.
Treatment results were, as far as excreted urinary Phosphate and Uric Acid concentrations were concerned, generally haphazard, with no clear pattern (Uric acid having wild swings). However, when the urinary Calcium concentration levels were examined, falls/dips were seen, generally starting at about 2 months of treatments. Irregular falls could persist for months (see Figures 4 & 5). These 1-2 month latent intervals# would seem to be in accord with the lag time estimated from the biopsy/Histopathology examination (see earlier).

See Figures 4 & 5. #Providing "auto control patterns."

Figure 4

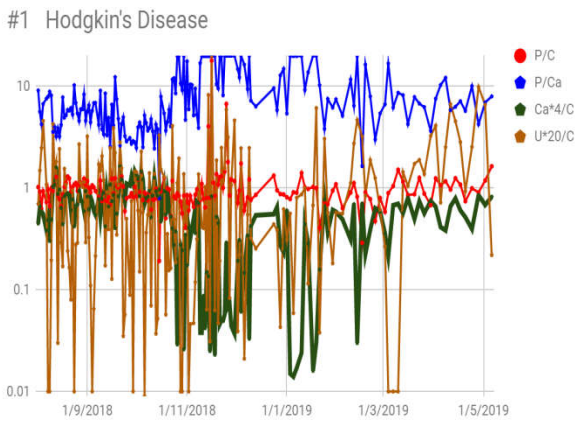
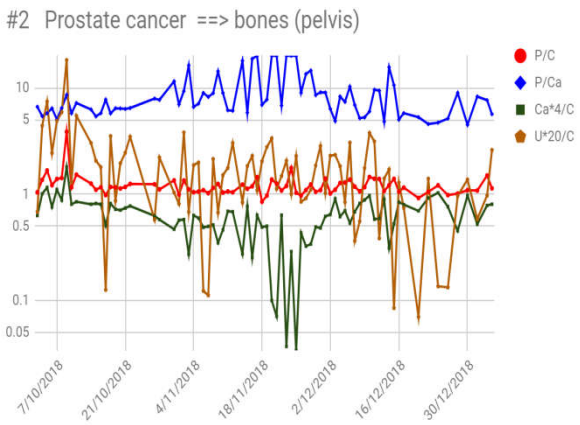


Figure 5



Figures 4 & 5: Spot Urine Phosphate concentration (Red), Uric Acid concentration (Brown) and Calcium concentration (Green) all referenced to same-day urinary Creatinine, sampled daily or with a longer interval. (The Blue lines are derived, Phosphate/Calcium, and are best ignored.) Note the falling Calcium concentration, starting ~1 - 2 month. The patient with Hodgkin's disease arrived grossly cachectic. His condition and weight improved and when seen about a year later, his weight had increased and he had returned to University activities, still taking Lithium. The man with Prostate cancer was barely able to walk because of pain. With treatment, the pain went. He was to continue the treatment, but was advised by someone else (using a defective test) that he was cured, so he stopped the treatment and suffered a relapse. After more treatments, and more recovered mobility, he went interstate and contact was lost. In figure 5, the Calcium concentration drop starts at about 4 weeks into the treatment. The Uric acid fall at about 2 months may reflect a reduced viable tumour bulk.

Figure 6

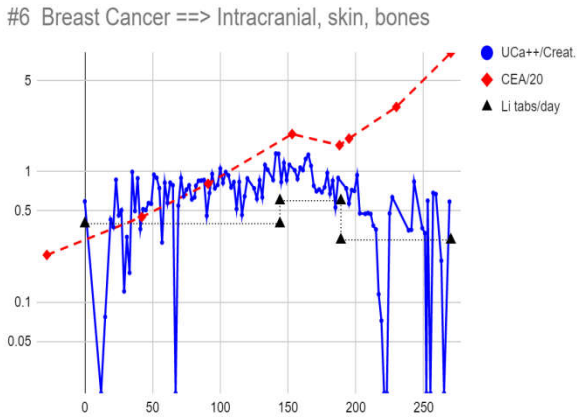


Figure 7

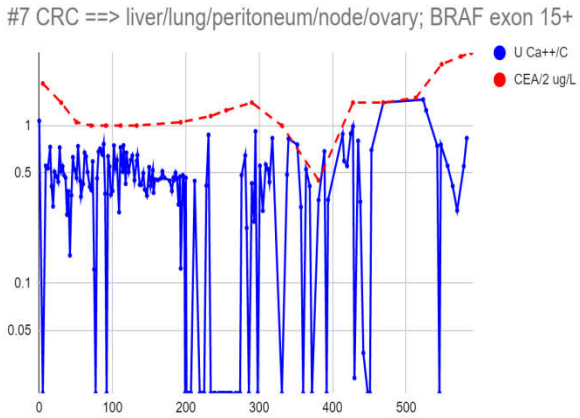


Figure 6: Graph of Urine Ca^{++}/Creatinine (blue, vertical axis) and CEA, with days (D, horizontal axis). The patient was started with 1 g Lithium carbonate (4x250 mg) on alternate days (black triangles). However, the markers (Serum Carcinoembryonic antigen µg/L [CEA, red] & Urine Calcium/C concentration, blue) indicated deterioration. The dose of Lithium was increased to 1.5 g/treatment day. The markers then indicated improvement (CEA fall, UCa^{++}/C fall). However, she complained of headaches* and decided to decrease the Lithium dose drastically (before ~D200) whereupon, the CEA marker started to rise. The Urinary calcium concentration then showed dips, probably a carry-over effect from the previous higher Lithium dose. She declined to increase the Lithium dose, had a catastrophic intra-cranial haemorrhage and died. The terminal headaches and deep calcium dips may have been due to intracranial/other tumour breakdown. *Not typical with Lithium

Figure 7: A 33 year old female with a mucoid carcinoma of the ileo-caecal valve (BRAF exon 15 mutation detected [=poor prognosis] with other gene studies favouring upper gastrointestinal origin; the mucus may aid an hypoxic state in the tumour cells, possibly aiding Necroptosis; Gong et al. 2017). Graphs are of Urine Ca^{++}/Creatinine (blue, vertical axis) and CEA (µg/L; red dash), with the days (horizontal axis). She came for hyperthermia (RHT) after having been diagnosed and given chemotherapy (Leucovorin, Fluorouracil & Oxaliplatin, later Fluorouracil, Capecitabine and Bevacizumab "Avastin") elsewhere in the previous year. Chemotherapy seemed successful, because subsequent PET studies showed no avidity*. The alternate-day Lithium protocol (1g/alternating treatment day) was accepted to augment the hyperthermia; the Li^+ treatment starting at day1 (D1). Whilst the serum CEA levels were low, they could provide a degree of monitoring usefulness. Very early (~D2-3) Calcium dips may indicate death of moribund cells. Dips at ~3 months were short-lived, becoming more prominent at about D200, with the CEA starting to rise appreciably at ~D520. She decided to halve the Lithium dose (to 500 mg Lithium carbonate/treatment day) at about D400 (after ~ 13 months Lithium treatment) and cease it ~D500 (~29 months from biopsy), the reason given was that she was concerned about the long-term effects of Lithium on her health. Urine testing became rare & ceased. During the interval whilst she was having 4 Lithium tablets/treatment-day (until ~D450) the CEA level showed no appreciable rise and the urinary Calcium dips were prominent. These features raise the possibility that cell proliferation was close to being in balance with cell destruction by Necroptosis, perhaps a dynamic state.

A pelvic Ultrasound examination ~8 months later revealed bilateral ovarian tumours (39x24x25 & 25x27x20 mm) which, when excised by a radical hysterectomy and oophorectomy ~4 months later, were metastatic mucinous carcinoma; immunophenotype SATB2 (strong), cdx2 (diffuse, strong) CK7 & 20 (both diffuse), probable colorectal primary. But after a further ~5 months she may have developed a small nodule in the scar of the surgical incision. Her post-operative CEA was 3.0 µg/L but, at the time of the feedback, (~6 months later) was 9.8 µg/L indicating [probably] larger metastases. A recent PET scan, (now with tracer uptake+), showed bony and lung metastases. She has now re-commenced Lithium treatment.

*The effective action of Lithium may be to reduce the access of glucose into the cells. It may also block access of the tracer [^{18}F]Fluorodeoxyglucose used for positron emission tomography (PET), producing a "false negative" result.

Given the probable poor prognosis associated with her cancer and (what appears to have been) dormancy of her ovarian (and other) metastases (possibly due to the Lithium treatment – whilst it lasted), her survival greater than 4 years (to date) is noteworthy, and has some similarities with the survival of a patient with a Glioblastoma (following).

Glioblastoma multiforme and Lithium

In 2017, a 77 Y old man had a fit. The MRI* indicated a Glioblastoma multiforme (GBM). There was operative de-bulking and biopsy. Then there was administered the obligatory Radiotherapy. That turned him into a Zombie. Chemotherapy brought on a life-threatening bone marrow failure, and so it was abandoned. Bevacizumab "Avastin" was considered, but rejected by the family. The alternate-day Lithium treatment protocol was suggested. The family agreed, and the wife supervised the treatment meticulously, maintaining the treatment for 4 months. However, her ability to cope flagged, so he moved into a nursing home and the Li^+ treatment ceased. Early in the nursing home, his cognition seemed to improve slightly, and the MRI at that stage also noted mild improvement (The Li^+ Rx unknown by the Radiologist.) After this, there was a slow decline. He died at 32 months post diagnostic MRI – a near record (*P*~0.01; Zhu, et al. 2017.)

Suggestion: All patients with GBMs could start on the alternate day Lithium protocol as soon as the scalp wound is closed. It should be continued as the only (specific) monotherapy until the 3-4 month MRI* review. Then, the therapists may consider the options. *Magnetic Resonance Imaging

HYPOTHESES

1. **The Alternate Day Lithium protocol**. The key enzyme for this phenomenon appears to be Bisphosphate nucleotidase (BPNT1). It splits the normal, toxic metabolite Phosphoadenosine phosphate (PAP) into Phosphate and Adenosine monophosphate (AMP). The former is dissipated, the latter contributes to AMP-Kinase, which has a key role in cellular metabolism (Herzig & Shaw, 2018) by maintaining mitochondrial biogenesis, and it also interacts with and suppresses/eliminates Thioredoxin-interacting protein (TXNIP, and possibly others), thereby stimulating the production &/or maintenance of the Glucose transporters (GLUTs; Augustin, 2010)) in the plasma membrane (Wu, 2013). Lithium may also block gluconeogenesis via phosphoenolpyruvate carboxykinase (Bosch, 1992). The action of Lithium is to **reverse** the sequence from BPNT1 on; the TXNIP level increases (augmented by Vitamin D3, Hamilton, 2014) and suppresses (a) GLUT1 action and both Glucose uptake and Clathrin-based destruction of GLUT1s and, (b) Reduces GLUT1 mRNA. (The latter may explain [in part] the long latent interval between the initiation of treatments and until the Lithium treatment has appreciable effects on tumours. The result is a glucose starvation, for which malignancies are vulnerable (Vaupel & Multhoff, 2021, as are activated inflammatory cells, Griffiths *et al.,* 2017 & Cheng *et al.,* 2014) with a resulting deficiency of Adenosine triphosphate (ATP) production causing a decline in the ability to power Apoptosis – hence the fall-back to Necroptosis.
2. **The Calcium changes**. A feature of Necroptosis is the damage to the plasma membrane of cells (Gong *et al.,*) In a resting cell, the cytosolic Calcium level is very low compared to that of (say) the serum, the cytosol level being 100-500 nM (Lawrie *et al.,* 1996): serum ~2.5 mM. This large Calcium differential means that if the plasma membranes of a large tumour mass are damaged by Necroptosis (Samson, 2020) extracellular Calcium can diffuse into the cell mass and be sequestrated, resulting in a fall in the output of Urinary Calcium. (Whilst the major store of Calcium is in the bones, movements to/from them are slow.)
3. **The alternate day Lithium protocol**. When Lithium is prescribed for Psychiatric patients, the serum/tissue levels are relatively constant and the level of PAP will be elevated ~continuously, meaning that it will be high enough to flood ("spill-over") the partially-inhibited BPNT1enzyme and thereby maintain a stream of AMP to sustain the need for GLUTs. With the alternate day administration; early on the treatment day, the toxic PAP will be low. With addition of Lithium, the inhibited enzyme will be primed to prevent the release of AMP to sustain the GLUTs, causing the glucose starvation. The inhibition of the GLUT1 mRNA may further slow the recovery of glucose uptake.
4. **Lithium Pharmacokinetics**. When a fasting ~70 Kg male consumed 1 g of Lithium carbonate as tablets (with water) the urine phosphate concentration rose after ~3.5 h. This provided some indication as to the time it took for (at least) one intracellular enzyme system dealing with phosphate re-uptake within the renal tubules to be inhibited. The same male had his serum Lithium measured ~45 minutes following the second bolus dose on a different day, producing a value of ~0.7 mmol/L, near the centre of a popular therapeutic range and below the quoted (0.8 mM LiCl for 50% inhibition of BPNT1 at 0.2 mM PAP). The rate of the BPNT1 enzyme reaction (i.e. the rate of AMP production) is increased by an increasing concentration of the substrate (PAP). (Spiegelberg *et al.,* 1999). This may provide another explanation for the alternate day protocol; the PAP level may be minimal just before the Lithium dose and the rate of AMP production is then minimal in the 2 day cycle, means that there will be less AMP released overall through the cycle.
5. **The usual prescribing protocol** for the cancer patients was to consume 500 mg Lithium carbonate as 2 x 250 mg tablets ~midday and a further 500 mg ~18:00 h. (This was based upon the protocol used by Janković for animals. Whilst a 1 g bolus can be ingested, there is an increasing risk of nausea, retching and vomiting as the dose rises above ~500 mg.) Since many patients were started with 1 g on **alternate** days, the **average** dose/day of 500 mg/day, is well below the typical maintenance dose of ~1 g/day for Psychiatric females (Traill, 1974; males had higher daily doses). If the alternate day dose is raised to 1.5 g per treatment day, effects may still be safe, but should be monitored.

CONCLUSION

Alternate day Lithium carbonate (as tablets) appears to halt/slow the progression of some tumours and, if continued indefinitely, may hold some tumours in a dormant-like state (a world first?).

An Histological study of a prostate cancer from a patient taking the alternate-day Lithium protocol, indicated that the degeneration in the cancer induced by the Lithium could be Necroptosis (a world first?) and the subsequent urine studies of Calcium concentrations were consistent with this assessment (a world first?).

This protocol for clinical cancer treatments has been monitored by ongoing measurements of the concentration of urinary Calcium (a world first?).

Many medical applications await the assessments and development in which the alternate-day Lithium protocol may confer benefits for patients, especially in the specialties of oncology and immunology.

REFERENCES

Augustin R. "The protein family of glucose transport facilitators: It's not about glucose after all." IUBMB Life. 2010 May; 62(5):31533

Bosch F, Rodriguez-Gil JE, Hatzoglou M et al. "Lithium inhibits hepatic gluconeogenesis and phosphoenolpyruvate carboxykinase gene expression." 1992 Feb 15;267(5):2888-93.

Cheng SC, Quintin J, Cramer RA, et al. “m Tor- and HIF-1α-mediated aerobic glycolysis as metabolic basis for trained immunity.” Science 2014 Sep 26; 345(6204):1250684.

Damjanovic M, Janković BD. “Suppression of experimental allergic encephalomyelitis by lithium cation.” Fed Proc 1984;43:1832

Frederick JP, Tafari AT, Wu SM et al. “A role for a Lithium-inhibited Golgi nucleotidase in skeletal development and sulfation” Proc Natl Acad Sci U S A. 2008 Aug 19;105(33):11605-12.

Gong YN, Guy C, Chase J, et al. “Biological events and molecular signalling following MLKL activation during necroptosis.” Cell Cycle 2017 16(19):1748-1760.

Griffiths HR, Gao D & Pararasa C. “Redox regulation in metabolic programming and inflammation.” Redox Biol 2017 Aug;12:5057.

Hamilton JP, Potter JJ, Koganti L et al. Hepatol Res. “Effects of Vitamin D3 stimulation interacting protein in hepatocellular carcinoma.” 2014 Dec;44(13):1357-66.

Herzig S & Shaw RJ. “AMPK: guardian of metabolism and mitochondrial homeostasis.” Nat Rev Mol Cell Biol 2018 Feb; 19(2):121-135

Hudson BH & York JD. “Tissue-specific regulation of 3'-nucleotide hydrolysis and nucleolar architecture.” Adv Biol Regul 2014 Jan;54:208-213.

Janković BD, Popesković L, Isaković K. Cation-induces immunosuppression: the effect of lithium on Arthus reactivity, delayed hypersensitivity and antibody production in the rat. Adv Exp Med Biol. 1979; 114:339-44

Janković BD, Isokovic K, Popeskovic L. Negative immune deviation induced by lithium cation. Immunol Lett 19801:203-208

Janković BD, Lenert P, Mitrović K. Suppression of experimental allergic thyroiditis in rats treated with lithium chloride. Immunobiology. 1982 May;161(5):488-93.

Kleinerman ES, Knowles RD, Blick MB, et al. “Lithium chloride stimulates human monocytes to secrete tumor necrosis factor/cachectin.” J Leukoc Biol. 1989 Nov;46(5):484-92.

Lawrie AM, Rizzuto R, Pozzan T, Simpson AW, “A role for calcium influx in the regulation of mitochondrial calcium in endothelial cells.” J Biol Chem 1996 May 3; 271(18):10753-9

Leist M, Single B, Castoldi A F et al. “Intracellular Adenosine triphosphate (ATP): a switch in the decision between apoptosis and necrosis.” J Exp Med. 1997 Apr 21;185(8):1481-6

Levine S & Saltzman A. “Inhibition of experimental encephalomyelitis by lithium chloride: non-specific effect or non-specific stress?” Immunopharmacology. 1991 Nov-Dec;22(3):207-13.

López-Coronado JM, Bellés JM, Serrano R et al. “A novel mammalian lithium-sensitive enzyme with a dual enzymatic activity, 3'-phosphoadenosine 5'-phosphate phosphatase and inositol-polyphosphate 1-phosphatase.” J Biol Chem 1999 Jun 4;274(23):16034-9.

Samson AL, Zhang Y, Geoghegan ND et al. “MLKL trafficking and accumulation at the plasma membrane control the kinetics and threshold for necroptosis.” Nat Commun. 2020 Jun 19;11(1):3151

Spiegelberg BD, Xiong J-P, Smith JJ et al. “Cloning and Characterization of a Mammalian Lithium-sensitive Bisphosphate 3-Nucleotidase Inhibited by Inositol 1,4-BisphosphateJ Biol Chem 1999 May 274(19):13619 -13628

Traill MA “The daily dose of Lithium carbonate related to the total body weight and the lean body weight in patients with affective disorders.” IRCS (Research on: Clinical Pharmacology and Therapeutics; Metabolism and Nutrition; Psychiatry and Clinical Psychiatry) 1974; 2:1055.

Vaupel P & Multhott G. “Revisiting the Warburg effect: historical dogma *versus* current understanding.” J Physiol 2021 Mar 599(6):1795-1757

Wu N, Zheng B,Shaywitz A et al. “AMPK-dependent degradation of TXNIP upon energy stress leads to enhanced glucose uptake via GLUT1.” Mol Cell. 2013 March 28; 49(6): 1167–1175.

Zhu P, Xianglin L. Du, Guangrong Lu and Jay-Jiguang Zhu. “Survival benefit of glioblastoma patients after FDA approval of temozolomide concomitant with radiation and bevacizumab: A population-based study.” Oncotarget 2017; 8(No 27): 44015-44

****