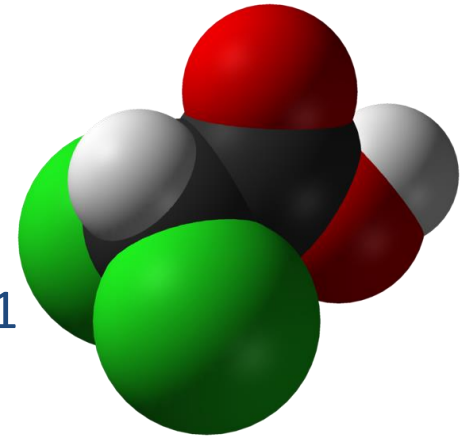


# **Metabolic Therapy with DCA (dichloroacetate)**

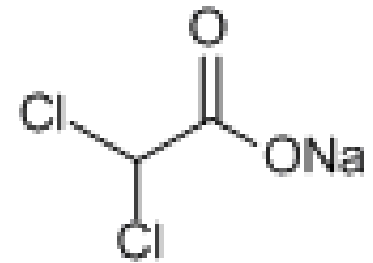
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Akbar Khan, M.D.

# What is DCA?

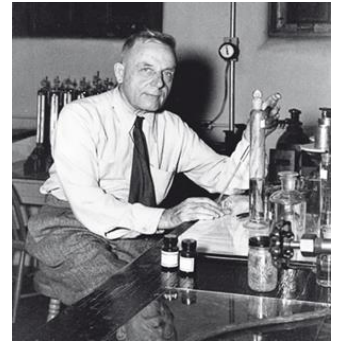


- a by-product of water chlorination<sup>1</sup>
- $C_2HCl_2NaO_2$
- dichloroacetic acid, sodium salt
- small molecule, like “salt and vinegar”
- highly water soluble
- penetrates blood-brain barrier<sup>2</sup>
- inhibits its own metabolism: GSTζ<sup>3</sup>

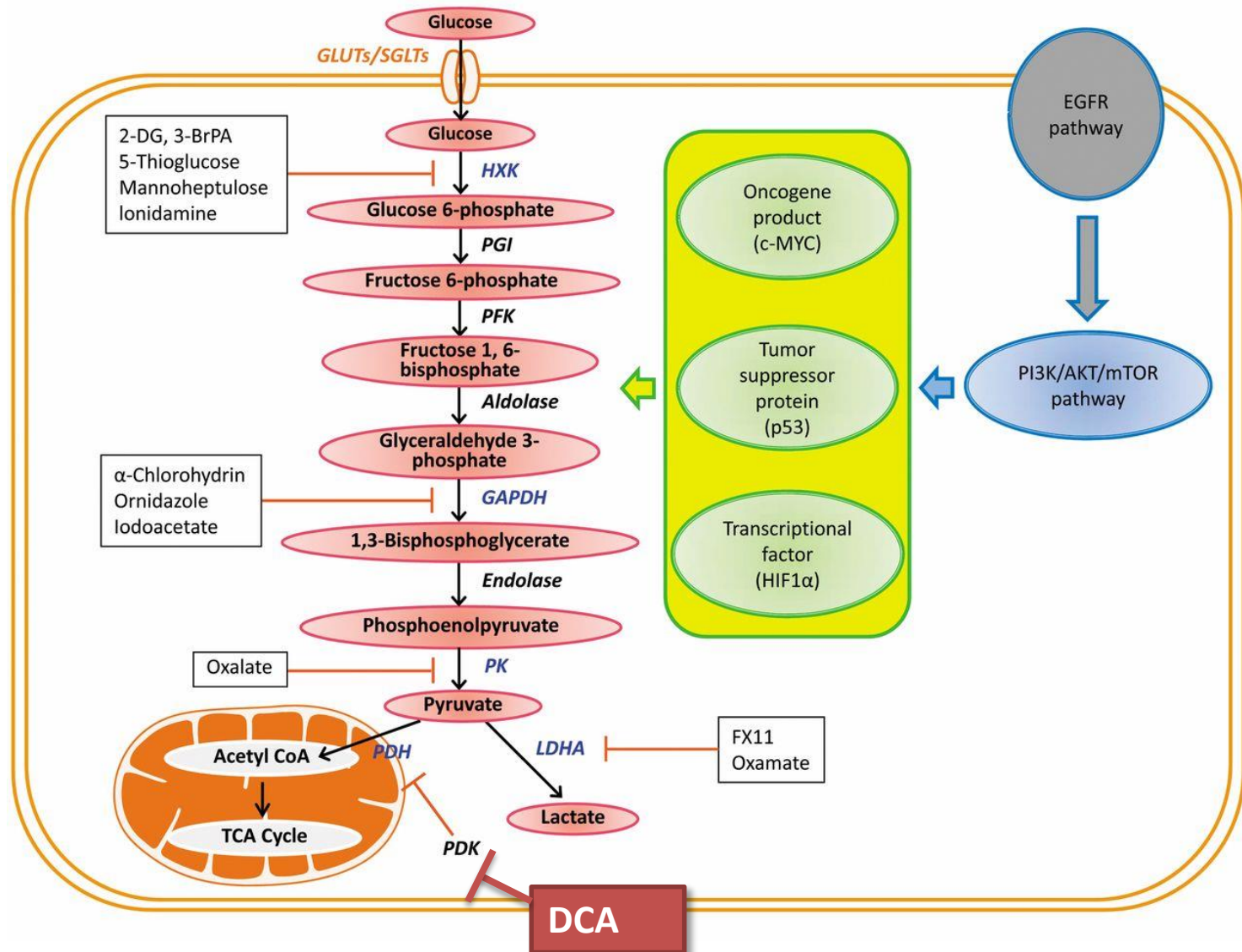


# Mechanism of Action

- inhibitor of PDH kinase (“PDK”) -> activates enzyme PDH resulting in a shift from glycolysis to glucose oxidation<sup>1</sup>
- cancer: aerobic glycolysis “Warburg effect”
- reduces mitochondrial membrane potential  $\Delta\phi_m$ , triggering apoptosis<sup>1</sup> (“natural cell suicide”)
- other mechanisms being investigated<sup>2</sup>



# Mechanism of Action



# Published *in vitro* Data

- original Michelakis paper: non-small cell lung, breast, glioblastoma<sup>1</sup>
- many others: colon<sup>2</sup>, prostate (alone and with radiation)<sup>3</sup>, ovarian<sup>4</sup>, neuroblastoma<sup>5</sup>, lung carcinoid<sup>6</sup>, cervix<sup>7</sup>, endometrial<sup>8</sup>, gastric (with 5-FU)<sup>9</sup>, hepatocellular (with sorafenib)<sup>10</sup>, head and neck SCC (with sulindac)<sup>11</sup>, melanoma<sup>12</sup>, T-cell lymphoma<sup>13</sup>, sarcoma<sup>14</sup> ...

# Un-published *in vitro* Data<sup>1</sup>

- potential strong synergism with **metformin** in breast ca + others (breast confirmed *in vivo*)
- potential strong synergism with **erlotinib** in non-small cell lung ca (confirmed *in vivo*)
- potential strong synergism with **taxane, platinum** + other chemos (platin. conf. *in vivo*)
- potential antagonism of chemos<sup>2</sup>
  - > unpredictable, need CS/CR assay

# Published *in vivo* Data

- **glioblastoma** (tumour shrinkage in 2 patients treated with DCA alone)<sup>1</sup>
- non-Hodgkins **lymphoma** (1 case of complete remission after chemo failure, DCA alone)<sup>2</sup>
- **cholangiocarcinoma** (1 case, response to DCA with omeprazole and tamoxifen)<sup>3</sup>
- **unknown primary** (dramatic pain reduction)\*<sup>4</sup>
- **met renal SCC** (cured by DCA + palliative XRT)\*<sup>5</sup>

# Un-published *in vivo* Data

- About 60% have partial response (palliation) in our experience<sup>1</sup>
- Occasional complete remission (about 1/50 – 1/100)<sup>2</sup>
- 32 M, met. melanoma (CT proven P.R.)
- 50 F, GBM with Sx/XRT, chemo x 1 yr (C.R. > 2 yrs)
- 47 F, ovarian stage 4, + 3 doses carboplatin (C.R. x 2 yrs. then recurrence)



# Un-published *in vivo* Data<sup>1</sup>

- 63 F, Non-Hodgkins Lymphoma (CT proven S.D.)
- 40 M, T-cell NHL w. CNS involvement (S.D. x 2 yrs)
- 44 M, angiosarcoma (S.D. x 1 yr)
- 10 M, pancreatic neuroendocrine (CT proven S.D.)
- 75 M, small cell lung (recur.) + 1 dose VP16 (cured)

# Un-published *in vivo* Data<sup>1</sup>

- 75 M, malig. fibrous histiocytoma (S.D. x 1.5 yrs)
- 80 M, TCC bladder (cysto proven shrinkage, cancelled radical cystectomy x 1 yr)
- cholangiocarcinoma (S.D. and P.R. in several cases)
- strong synergism with honokiol in CLL and others
- strong synergism with fermented wheat germ extract in several cancers (AveUltra™ or Avemar™)
- PSA reduction in castration-resistant prostate ca

# Common Side Effects\*

- Approx. 40% have no side effects
- **All reversible, incidence depends on dose**
- **Neurological and G.I. primarily**
- Peripheral neuropathy ~20%
- Fatigue / Sedation ~ 20%
- Confusion/reduced memory ~20%
- Tremors

# Side Effects

- Hallucinations
- Agitation
- Mood changes – anxiety / depression
- Heartburn
- Nausea (rare vomiting)
- Increased tumour pain (temporary)
- Asymptomatic AST / ALT / GGT increase (1-2%)

# Good Side Effects / Benefits

- Safe in renal failure (liver metabol, no renal tox)
- Good in angina & heart failure ( $\uparrow$  pumping efficiency with no  $\uparrow$  in oxygen demand)<sup>1</sup>
- Shortens QT interval (safe with  $\uparrow$  QT drugs)<sup>2</sup>
- Improves diabetes (mild glucose  $\downarrow$ )<sup>3</sup>

# Drug Interactions

- Minimal drug interactions in our experience<sup>1</sup>
- Not metabolized by P450 system (GST $\zeta$ )
- Caution with cannabinoids and other CNS drugs that cause delirium (start low,  $\uparrow$  slowly)

# Need for Natural Medicines

- ↓ Side effects (neuropathy/encephalopathy):
  - R-alpha lipoic acid 150mg tid (avoid overlapping with XRT/chemo)
  - acetyl L-carnitine 500mg tid
  - benfotiamine (lipid sol vit B1) 80mg bid
- Synergistic antineoplastic effects:
  - Dr. Neil McKinney ND, “mitochondrial rescue” <sup>1</sup>
  - ALC, R-ALA, B1, Co-Q10, I3C, quercetin etc.

# Sample Protocol (oral)

- DCA 15-25mg/kg/d, bid or tid, 14d on/7d off
- R-ALA 150mg tid, benfotiamine 80mg bid, ALC 500mg tid
- CBC, lytes, BUN, creat, Ca, albumin, bili (T+D), **AST, ALT, ALKP, GGT**, LDH, glucose, q 1 wk x 4 then reduce if ok
- Relevant tumour marker(s) q 4 wks
- If GI upset, try pantoprazole 40mg po qd



# Protocols With Chemo

- potential strong synergism with chemos, but also potential antagonism of chemos<sup>1</sup>
- Protocol must be individualized along with specific chemo cycle
- If CS/CR assay conducted, use appropriate combo per assay result
- If no CS/CR assay, avoid overlapping DCA and chemo for safety (DCA between chemo doses)

# Summary

- DCA may be effective for any cancer type
- DCA may be effective for chemo-resistant cancers
- DCA has no life-threatening side effects<sup>1</sup>, is not immunosuppressive, no effect on cell counts
- DCA reduces its own metabolism ( $T_{1/2}$  increases)
- Increasing side effects possible with stable dose
- For oral DCA, cyclic therapy appears to be best)

# Summary

- Main limiting side effect is neuropathy
- Natural neuropathy prevention is essential
- if oral DCA causes side effects, DCA iv may be ok
- Watch the liver enzymes
- DCA works best in combination therapy (multi-targeted approach)
- Palliative benefits are significant
- Occ complete remission, stage 4 cancer (1-2%)<sup>1</sup>

The image features a classic hypnotic spiral background, consisting of concentric circles that create a sense of depth and motion. The colors are primarily red and black, with the spiral transitioning from a dark red at the center to a black at the outer edges. Overlaid on this background is the text "That's all Folks!" in a white, elegant cursive font. The text is positioned diagonally across the center of the spiral, starting from the lower-left and ending at the upper-right. The central part of the spiral is a solid dark blue circle, which serves as a focal point for the text.

*That's all Folks!*