



**EVEN LOW  
HANGING  
FRUIT**

**CAN BE  
DIFFICULT  
TO REACH**

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1. no conflicts of interest
2. i will be discussing off label use of drugs.
3. no herbal, nutritional supplements, or non-FDA, non-EMA drugs.



eleven core principles of  
repurposing drugs  
for cancer treatment  
with three recent  
examples.

1 2 3 4 5 6 7 8 9 10 11

repurposing is really **unrepurposing**.

recognize attributes -

match drug attribute to a cancer

physiological attribute.

1 2 3 4 5 6 7 8 9 10 11

## constraints:

cheap, well understood, low risk.

DIYers. no profit. regulatory difficulties.

peer criticism, institutional restrictions,

legal fears, poor understanding of

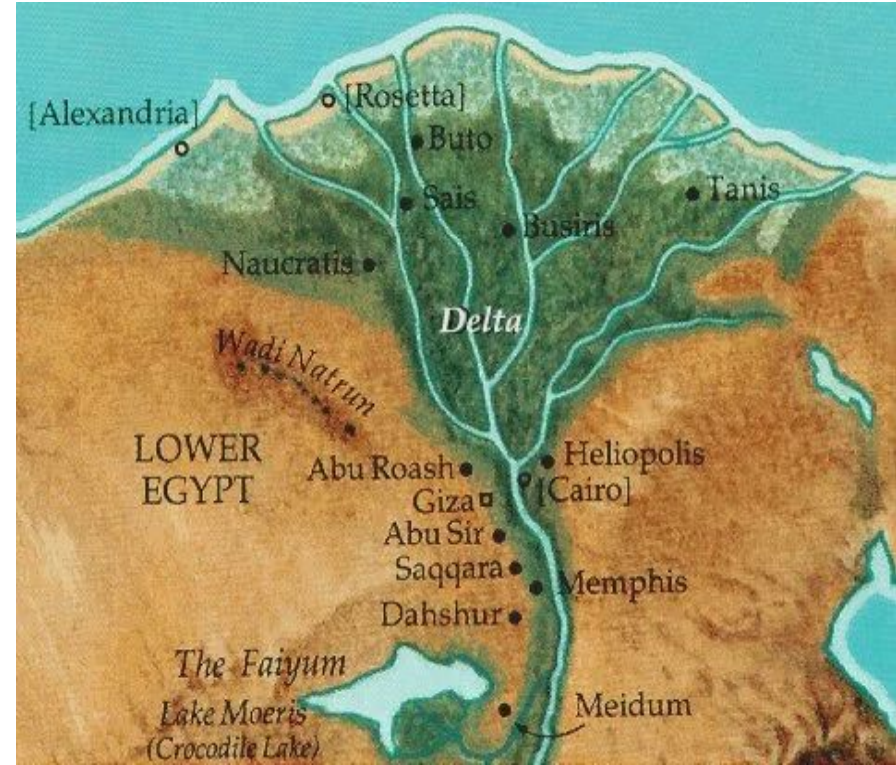
cancer physiology & drug action



1 2 3 4 5 6 7 8 9 10 11

Nile distributary  
problem. example:

anlotinib - multi-target TKI.  
targets VEGF receptor, FGF  
receptor, PDGF receptor,  
and stem cell factor receptor  
(c-Kit) - 3.3 month PFS was called an **“an effective regimen”**  
in NSCLC.



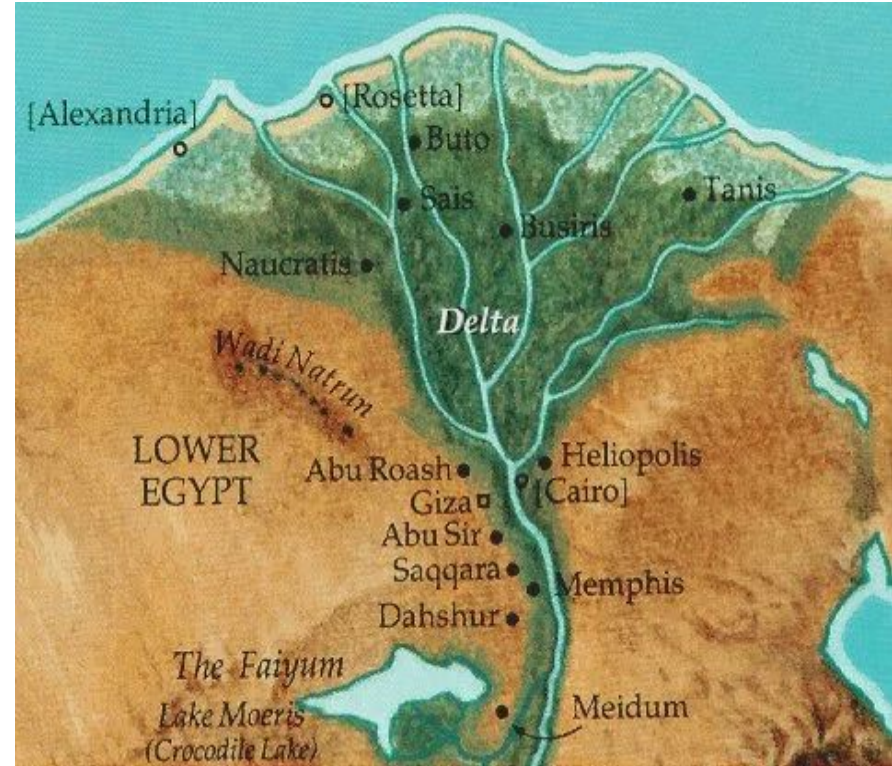


1 2 3 4 5 6 7 8 9 10 11

# Nile distributary Problem.

Cancers (Basel). 2019;11(7). pii: E892  
Future Sci OA. 2019;5(6):FSO390.

horizontal  
intercellular transfer of  
resistance, mitochondrial  
& extrachromosomal circular DNA



1 2 3 4 5 6 7 8 9 10 11

cancers have no achilles' heel.

[ like all well engineered machines ]

cf. basal cell carcinoma

1 2 3 4 5

6 7 8 9 10 11

shaping operation

clean room,  
sterile instruments,  
food & laundry service,  
anesthesia,  
blood bank,  
administration, finance, accounting

decisive operation

resection  
(irradiation)

1 2 3 4 5 6 7 8 9 10 11

in cancer treatment,

repurposed drugs tend to be

shaping operations

1 2 3 4 5 6 7 8 9 10 11

- a] 1 thru 5 above imply need for polypharmacy.
- b] meds must be coordinated.  
cf. 3 locks problem.
- c] celecoxib, chloroquine, disulfiram, metformin, statin, valproate failures.....

1 2 3 4 5 6 7 8 9 10 11

if one tries to  
hold onto everything,  
one ends by holding onto  
nothing.

[ overavoid SE, gross underdosing i.a. ]



1 2 3 4 5 6 7 8 9 10 11

chess aphorism:

all moves create strengths and  
weaknesses

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[our interventions have pro tumor growth  
aspects plus anti-tumor growth aspects]

1 2 3 4 5 6 7 8 9 10 11

cancers are not passive  
recipients of our interventions.  
every growth retarding intervention  
engages compensatory growth  
restoring reaction.

1 2 3 4 5 6 7 8 9 10 11

surgery, irradiation, and cytotoxic  
chemotherapies deliver a  
get-up-and-go signal. cancers exhibit  
accelerating aggressiveness  
over time.

1 2 3 4 5 6 7 8 9 10 11

mechanism based  
or  
empirically based

# 1 2 3 5-ALA CAALA Regimen

<u>drug</u>	<u>marketed</u>	<u>function in CAALA</u>
ciprofloxacin	ABX	impair mitochondria
deferiprone	Fe reduction	less PpIX to heme
5-fluorouracil	cytotoxin	mitochondria damage
febuxostat	uricosuric	inhibit 5-ALA efflux

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Kast et al. Augmentation of 5-Aminolevulinic Acid Treatment of Glioblastoma by Adding Ciprofloxacin, Deferiprone, 5-Fluorouracil and Febuxostat: The CAALA Regimen. Brain Sci. 2018;8(12). pii: E203.

1 2 3

1. methylene blue inhibits NLRP3 inflammasome function.
2. NLRP3 essential in MDS marrow destruction

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Kast RE. Inhibiting the NLRP3 Inflammasome With Methylene Blue as Treatment Adjunct in Myelodysplasia. *Front Oncol.* 2018;8:280.



1

2

3

CUSP9v3... NCT02770378

Principal investigator -

Marc-Eric Halatsch, MD, PhD

Ulm University Medical Center, Ulm, Germany

nine repurposed general medicine drugs to augment temozolomide in recurrent glioblastoma

1

2

3

# CUSP9v3... NCT02770378

- |   |                    |
|---|--------------------|
| 1. aprepitant.....80 mg x 1                     | [ lorazepam        |
| 2. auranofin.....3 mg x 2                       | hydromorphone      |
| 3. captopril.....50 mg x 2                      | loperamide         |
| 4. celecoxib.....400 mg x 2                     | V-8, miso, broth ] |
| 5. disulfiram.....250 mg x 2                    |                    |
| 6. itraconazole....200 mg x 2                   |                    |
| 7. minocycline.....100 mg x 2                   |                    |
| 8. ritonavir.....400 mg x 2                     |                    |
| 9. sertraline.....100 mg x 2                    |                    |
| 10. temozolomide...20 mg/m <sup>2</sup> BSA x 2 |                    |

1 2 3

## CUSP9v3...

good tolerability

PFS12 = 50%

PFS18 = 40%

no drug related withdrawals

but ensemble not cheap

grade 1 or 2 fatigue was common

F-22A = \$68,000 / hour



F-16 = \$25,500 / hour



F-35 = \$30,000 / hour



UK's Merlin Mk 3, £42,000 / hour



<https://clue.io/repurposing>

1. **CUSP9v3** for GB
2. **ADZT** aprimilast, dapsone, zonisamide, telmisartan to augment bevacizumab
3. **5aai** 5-ALA augmented irradiation for DIPG
4. **MB** methylene blue for myelodysplasia
5. **ABC7** for breast cancer capecitabine, quetiapine, pirfenidone, rifabutin, metformin, propranolol, agomelatine, ribavirin
6. **CAALA** cipro, 5-FU, febuxostat, deferiprone to augment 5-ALA
7. **EIS** itraconazole, metformin, naproxen, pirfenidone, quetiapine, rifampin for GB
8. **DFR** dapsone, fenofibrate, ribavirin to lower G-CSF function in GB
9. **MTZ** minocycline, telmisartan, zolidronic acid in GB
10. **PMC** plerixafor, mirtazapine, clotrimazole for GB





even low hanging  
fruit can be  
difficult to reach