# Latest news about drug repurposing in oncology #23

20 August 2024

Drug repurposing is a strategy for identifying new uses for approved drugs, outside the scope of the original indication. It is one of the focus areas of the Anticancer Fund.

Below, we have listed recent findings about the repurposing of generic drugs in oncology. Our intention is to help bring these findings to the attention of the broader cancer research community.

Being listed is no endorsement of the results and conclusions of the article. All articles need to be critically assessed and viewed in their broader context.

Please get in touch if you're interested in discussing research based on the findings presented below (info@anticancerfund.org).

## Top story

### NBS1 Lactylation Is Required For Efficient DNA Repair And Chemotherapy Resistance

Published in Nature

One of the mechanisms associated with chemotherapy resistance is enhanced DNA repair processes which stops the induction of apoptosis in cells damaged by cytotoxic drugs. In this study by Chen et al, they delved into the role of lactate, a by-product of the anaerobic metabolism of cancer cells (aka the Warburg effect). In a series of experiments, including with PDX models, the authors show that lactate-driven lactylation of NBS1 promotes homologous recombination (HR)-mediated DNA repair. Lactylation of NBS1 at lysine 388 (K388) results in the accumulation of HR repair proteins at the sites of DNA double-strand breaks. Furthermore, the authors use clinical data to show that the overall survival rate of neoadjuvant chemotherapy patients with high levels of NBS1 K388 lactylation

and lactate dehydrogenase A (LDHA) was lower than of other patients. Cell lines and mouse models were used to genetically deplete LDHA, showing improved response to chemotherapy - results which were confirmed using stiripentol, an inhibitor of LDHA used to treat some forms of epilepsy. These data suggest that inhibition of lactate generation using a repurposed drug may be a strategy to overcome chemotherapy resistance in some cancers.

**Clinical data**

*Clinical trials*

Atorvastatin for Anthracycline-Associated Cardiac Dysfunction: The STOP-CA Randomized Clinical Trial
Published in JAMA
This randomized Phase II trial investigated the addition of atorvastatin to anthracycline-based chemotherapy in 300 patients with lymphoma to assess its potential in reducing anthracycline-induced cardiac dysfunction. The incidence of the primary outcome - proportion of patients with an absolute decline in LVEF of 10% prior to chemotherapy to a final value of less than 55% - was significantly reduced in the patient group receiving atorvastatin compared to the placebo group (9% vs 22%, P=0.002) at 12-month follow-up. Similarly, the secondary outcome - proportion of patients with absolute decline in LVEF of 5% from prior to chemotherapy to a final value of <55% - was also reduced in the atorvastatin group (13% vs 29%, P=0.001) at 12-month follow-up. These results demonstrate that atorvastatin may reduce the incidence of cardiac dysfunction in lymphoma patients treated with anthracycline-based chemotherapy, indicating its potential role in preventing cardiac systolic dysfunction. However, this strong evidence requires confirmation in a Phase III trial.

Phase 1 Study Of High-Dose DFMO, Celecoxib, Cyclophosphamide And Topotecan For Patients With Relapsed Neuroblastoma: A New Approaches To Neuroblastoma Therapy Trial
Published in British Journal Of Cancer
Hyperactivated Myc is the principal oncogenic driver of refractory or relapsed neuroblastoma, primarily by regulating Odc to increase intratumoral polyamines. Given this mechanism, tumors like neuroblastoma may be partially vulnerable to therapeutics targeting polyamine depletion. In this Phase I trial involving 24 patients with advanced neuroblastoma, the Odc inhibitor DFMO was combined with celecoxib and cyclophosphamide/topotecan chemotherapy to assess tolerability. The authors concluded that oral DFMO, administered at high doses up to 9000 mg/m2/day, was tolerable when combined with chemotherapy and demonstrated activity in patients with refractory or relapsed neuroblastoma. The two-year PFS and OS rates for the entire cohort were 29,5%

and 58,3%, respectively, with 3 patients remaining progression-free at >4 years without requiring additional therapy. These findings suggest that high-dose DFMO (Eflornithine) has potential beyond its current use in high-risk neuroblastoma prevention, warranting further investigation. Currently, a randomized Phase II trial is being conducted to evaluate DFMO in combination with chemoimmunotherapy (NCT03794349).

Aspirin vs Placebo as Adjuvant Therapy for Breast Cancer: The Alliance A011502 Randomized Trial

Published in JAMA

Observational studies and randomized trials on cardiovascular disease have suggested that aspirin use may be associated with improved breast cancer survival. To further investigate this potential benefit, the authors conducted a prospective Phase III trial to determine whether aspirin (300 mg/d) reduces the risk of invasive cancer events in breast cancer survivors. Primary outcome was invasive disease-free survival, with overall survival (OS) as secondary. Although there were numerically more all invasive disease-free survival events in the aspirin group compared to the control group (141 vs 112, HR=1.27), the difference was not statistically significant (P=0.06). Additionally, no difference was observed in OS and adverse events between the two groups. Consequently, this trial could not show that daily aspirin intake can prevent breast cancer recurrence and improve survival. If other ongoing trials in breast cancer yield similar outcomes, it could be recommended to reconsider the use of daily aspirin as adjuvant breast cancer therapy.

Improved Survival With Adjuvant Cyclooxygenase 2 Inhibition in PIK3CA-Activated Stage III Colon Cancer: CALGB/SWOG 80702 (Alliance)

Published in Journal Of Clinical Oncology

The primary endpoint of the clinical trial investigating the use of the cyclooxygenase-2 (COX-2) inhibitor celecoxib as adjuvant therapy for stage III resected colorectal cancer was previously reported. It showed no significant difference in disease-free survival (DFS), despite observational studies suggesting a lower risk of recurrent disease with celecoxib compared to non-use. This study focuses on evaluating DFS and OS in patients receiving celecoxib in addition to standard adjuvant chemotherapy, with analysis based on PIK3CA mutational status, which is hypothesized to predict a better response to COX-2 inhibition. The authors showed that patients with PIK3CA gain-of-function mutations treated with celecoxib had improved DFS and OS compared to those with PIK3CA wildtype group. Although the interaction test for DFS was not significant (P=0.13), the test for OS was statistically significant (P=0.03). These results suggest that use of COX-2 inhibitors in molecularly targeted patients might have therapeutic value.

[High Dose Vitamin D Supplementation Does Not Improve Outcome In A Cutaneous Melanoma Population: Results Of A Randomized Double-Blind, Placebo-Controlled Study (Vidme Trial)]
Published in The British Journal Of Dermatology
This Phase III trial (n=436) investigates whether high dose vitamin D supplementation reduces melanoma relapse in patients with curatively resected cutaneous melanoma. In vitro and in vivo studies have suggested that Vitamin D may exert anti-carcinogenic effects, protecting against cutaneous melanoma. The primary endpoint was relapse-free survival (RFS), with secondary endpoints including melanoma-related mortality, overall survival and the evolution of 25-hydroxy vitamin D serum levels over time. Monthly high dose vitamin D supplementation (100,000 IU cholecalciferol) increased 25-hydroxy vitamin D serum levels after 6 months of supplementation and was steady throughout the treatment period. However, the event rate for RFS at 72 months showed no significant difference between the vitamin D supplemented arm and the placebo arm (26.51% vs 20.70%, hazard ratio= 1.27, P=0.32). Additionally, melanoma and non-melanoma related mortality were similar in both arms, indicating that vitamin D supplementation could not reduce the risk of cutaneous melanoma relapse or mortality. This makes it unlikely that vitamin D has significant activity in this patient population.

*Cases*

[The Addition Of Chloroquine And Bevacizumab To Standard Radiochemotherapy For Recurrent Glioblastoma Multiforme]
Published in British Journal Of Neurosurgery
This small retrospective study (n=42) investigated the addition of chloroquine (HCQ) and bevacizumab (BEV) to an adjuvant-radiochemotherapy (aRCT) in patients with recurrent-glioblastoma based on overall survival (OS) and post-recurrence-survival (PRS). Patients receiving additional treatment (aRCT+HCQ+BEV (n=4) or aRCT+BEV (n=5)) showed a trend towards longer median OS compared to the control group, although this difference was not statistically significant in the small sample. Further clinical studies with lager samples sizes are necessary. Notably, the median PRS was statistically significantly better in patients treated with aRCT+HCQ+BEV compared to the control group (23.92 vs 9.63 months, P=0.022), highlighting the synergistic effect of HCQ+BEV in treatment. Median PRS for patients receiving aRCT+BEV was 12.97 months.

**Preclinical data**

Clinical Drug Screening Reveals Clofazimine Potentiates The Efficacy While Reducing The Toxicity Of Anti-Pd-1 And Ctla-4 Immunotherapy
Published in Cancer Cell
To improve the antitumor potency of the dual anti-PD-1 and CTLA-4 immune checkpoint blockade (ICB) therapy – a major topic in clinical oncology – they screened approximately 3000 FDA-approved drugs using organotypic tumor spheroids to identify potential third agents for optimizing this therapy. Clofazimine emerged as the most effective candidate, demonstrating the highest synergistic effect and the ability to overcome anti-PD-1+CTLA-4 ICB treatment resistance while reversing lethal immune-related adverse events (irAEs). Mechanistically, they showed that clofazimine activates the E2F1 pathway in CD8+ T cells to overcome resistance and attenuates pathogenic Th17 cell differentiation to abolish irAEs. These promising findings have prompted the planning of a Phase Ib clinical trial assessing the safety and efficacy of clofazimine added to anti-PD-1/ CTLA-4 ICB treatment.

Retinoic Acid Receptor Activation Reprograms Senescence Response And Enhances Anti-Tumor Activity Of Natural Killer Cells
Published in Cancer cell
The study investigates how retinoic acid receptor (RAR) activation influences the senescence response in prostate cancer (PCa) cells. The authors identified RAR agonists like adapalene, which is currently used in the clinic to treat mild-to-severe acne, as effective in inducing a strong, p21-driven senescence response in PCa cells. When combined with the chemotherapy drug docetaxel, RAR agonists are more effective than single treatments in inducing senescence. Additionally, this approach reprograms the senescence-associated secretory phenotype (SASP) from tumor-promoting to tumor-suppressive. In vivo models further demonstrated that this reprogramming enhances the recruitment and activity of natural killer cells, leading to improved tumor clearance. The findings suggest that combining RAR agonists with standard treatments could enhance the anti-tumor immune response in “immunologically cold” tumors in PCa, and therefore the efficacy of immunotherapies.

Adjuvant Cox Inhibition Augments Sting Signaling And Cytolytic T Cell Infiltration In Irradiated 4T1 Tumors
Published in JCI Insight
This in vitro study examines the effects of immune therapy with pan-nitric oxide synthase (NOS) inhibitors and pan-COX inhibitors (like indomethacin) combined with radiation on radiation therapeutic efficacy. The findings demonstrate that this combined treatment effectively reduces primary tumor growth and lung

metastasis in aggressive 4T1 TNBC tumors (expressing high COX2), partly through an enhanced antitumor immune response. Mechanistically, the study shows that cox inhibition augments lymphoid infiltration in radiation-indomethacin-treated 4T1 tumors and enhances STING signaling and type I IFN gene expression. In diseases such as TNBC with a high unmet need, improving radiation efficacy is important, underscoring the need for further clinical investigation.

## Exhaustive In Vitro Evaluation Of The 9-Drug Cocktail Cusp9 For Treatment Of Glioblastoma

Published in Computers In Biology And Medicine

This in vitro study assessed whether any of the 511 possible subsets of the 9-drug cocktail CUSP9 could achieve outcomes comparable to or better than the full regiment for treating glioblastoma. All subsets were tested in combination with the standard-of-care drug temozolomide on clonal cultures of glioma-initiating cells. Using live-cell imaging and cell viability analyses, the authors demonstrated that multiple lower-order drug combinations were equally effective as the full CUSP9 cocktail, suggesting the potential for a simplified regimen. Notably, a specific 4-drug subset consisting of auranofin, disulfiram, itraconazole, sertraline proved effective, reducing cell growth, changing cell morphology, and increasing the number of apoptotic-like cells within 4-28h of treatment compared to untreated cells. Additionally, cell viability was significantly decreased after 68h.