Latest news about drug repurposing in oncology #15

1 April 2022

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 research context.

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

Top story

Inflammatory fibroblasts mediate resistance to neoadjuvant therapy in rectal cancer

Published in Cancer Cells

Inflammatory cancer-associated fibroblasts (iCAFs) are associated with poor chemoradiotherapy response in rectal cancer. Using both mice models and patient-derived tumour organoids and primary stroma cells, this study shows that interleukin-1a(IL-1a) polarises cancer-associated fibroblasts toward the inflammatory phenotype but also triggers oxidative DNA damage which in turn leads to stromal cell senescence in response to radiation. Furthermore, iCAFs are associated with poor prognosis in rectal cancer patients. Blockade of IL1 signalling prevents iCAF senescence upon irradiation, including through the use of the repurposing candidate anakinra, and improved therapy response. A small

phase I clinical trial (NCT04942626) is testing this hypothesis in rectal cancer patients.

Clinical data

Clinical trials

Randomized trial of topical ascorbic acid in DMSO versus imiquimod for the treatment of basal cell carcinoma
Published in Biomedicine & Pharmacotherapy
Topical treatment of basal cell carcinoma using imiquimod is an established and effective therapy for patients with low-risk superficial disease. In this small (n=25) Phase I clinical trial imiquimod was compared to topical ascorbic acid (30% solution) for 8 weeks. Post-treatment biopsy of lesions showed complete resolution of 13/15 (86.7%) in the ascorbic acid group, while 8/14 (57.1%) lesions in the imiquimod group were resolved. Furthermore, ascorbic acid was associated with fewer adverse effects - 70% of patients in the imiquimod group showed residual hypopigmentation at 30 months follow up versus 0% in the ascorbate group. These results are supportive of further clinical trial investigation in this very common cancer. Improving the formulation to make it stable and usable on a larger scale will be an essential step before moving forward though.

Phase I/II trial of enzalutamide and mifepristone, a glucocorticoid receptor antagonist, for metastatic castration-resistant prostate cancer
Published in Clinical Cancer Research
Data suggests that increased glucocorticoid receptor (GR) expression compensates for reduced androgen receptor activity in prostate cancer cells treated with androgen reception signalling inhibition and may therefore be a therapeutic target to delay the emergence of resistance and progression to castrate-resistant prostate cancer (CRPC). This randomised controlled phase I/II trial assessed the safety, pharmacokinetic impact, and efficacy of the GR antagonist mifepristone (Mif) in combination with enzalutamide vs enzalutamide alone for CRPC. A 25% dose reduction in enzalutamide, when combined with mifepristone resulted in equivalent drug levels compared to full dose enzalutamide and was well tolerated. However, the combination did not delay time to PSA, radiographic or clinical PFS and therefore the trial was terminated early due to futility.

Phase I Study Evaluating Dose De-escalation of Sorafenib with Metformin and Atorvastatin in Hepatocellular Carcinoma (SMASH)
Published in The Oncologist
This phase I dose de-escalation study aimed to assess the tolerability, safety,

pharmacokinetics (PK), and efficacy of sequentially decreasing doses of sorafenib in combination with atorvastatin and metformin in patients with advanced hepatocellular carcinoma (HCC). The rationale for this combination in HCC includes the individual inhibitory effects of these drugs against chronic hepatitis and cirrhosis as well as their *in vitro* potential to re-sensitize HCC cells to the action of sorafenib. Patients were recruited in four cohorts of 10, from 800 mg sorafenib to 200 mg in decrements of 200 mg. Based on the safety data as well as PK analysis, the sorafenib dose for further trials in advanced HCC is 600 mg daily when combined with 10 mg of atorvastatin and 500 mg sustained-release metformin twice daily.

A phase II study of sequential decitabine and rapamycin in acute myelogenous leukemia
Published in Leukemia Research
This phase II study, (n=26), compared sequential decitabine followed by rapamycin (sirolimus) with decitabine alone in patients with relapsed or refractory acute myelogenous leukemia (AML) or newly diagnosed AML patients who were >65 years old and not eligible for intensive induction regimens. The study did not meet its primary endpoint of a significant improvement in composite CR rate (CR plus CR with incomplete count recovery) with the combination treatment - showing 33% compared to a historical CR rate of 25% with decitabine alone. Notably, 50% of subjects in the new diagnosed group achieved a composite CR which is significantly higher ($p = 0.02$) than the rate of 25% with decitabine alone, although this was not a primary outcome for the study.

Observational studies

Angiotensin blockade therapy and survival in pancreatic cancer: a population study
Published in BMC Cancer
Large, well-designed retrospective studies can provide valuable hypothesis-generating data for further exploration. In this study, the authors looked at the relationship between pancreatic cancer and post-diagnosis use of angiotensin II receptor blockers (ARBs) or angiotensin I converting enzyme (ACE) inhibitors. 8,158 patients were included, including 36% diagnosed with metastatic disease and 20% whom were treated with surgical resection. Compared to otherwise similar patients, those exposed to ARBs after pancreatic cancer diagnosis experienced 20% lower mortality risk (HR=0.80; 95% CI: 0.72, 0.89). Those exposed to ACE inhibitors during the first three years of survival after PC diagnosis experienced 13% lower mortality risk (HR=0.87; 95% CI: 0.80, 0.94) - this survival advantage attenuated after surviving three years (HR=1.14; 95% CI: 0.90, 1.45). These results are in line with some preclinical studies and are

supportive of the prospective clinical trials currently assessing these drugs as treatments.

Preclinical data

The anthelmintic drug niclosamide induces GSK-β-mediated β-catenin degradation to potentiate gemcitabine activity, reduce immune evasion ability and suppress pancreatic cancer progression
Published in Cell Death & Disease
Niclosamide is one of many anti-helminthic drugs which has potential as a repurposed drug in oncology. In this paper Guo and colleagues explore the actions of the drug *in vivo* against pancreatic cancer. Results showed that it reduced tumour growth and the development of metastases. Multiple mechanisms of action are outlined, including increased apoptosis, reduction of immune evasion (via PDL1 downregulation) and synergy with gemcitabine chemotherapy - all mediated by via targeting β-catenin.

Fungal mycobiome drives IL-33 secretion and type 2 immunity in pancreatic cancer
Published in Cancer Cell
Building on previous work looking at the impact of the pro-tumour immune milieu in pancreatic cancer, particularly TH2 cells and innate lymphoid cells 2 (ILC2), this preclinical study shows that intratumour fungal species increase IL-33 secretion which results in TH2 and ILC2 trafficking to the tumour. Blocking IL-33 reduces tumour growth via reduction in Th2 and ILC2 recruitment to the tumour microenvironment. Mice treated with oral anti-fungal treatment (amphotericin B) showed reduced tumour growth and increased survival. While it is too early to be considering assessing this clinically, this is a novel and interesting study that warrants further preclinical study.

ALDH1A1 Gene Expression and Cellular Copper Levels between Low and Highly Metastatic Osteosarcoma Provide a Case for Novel Repurposing with Disulfiram and Copper
Published in Sarcoma
Osteosarcoma is a cancer characterised by high levels of tumour heterogeneity, a lack of molecular subtypes and a disease in which clinical progress has been stalled for many years. In this paper Mandell and colleagues explore ALDH1 expression in murine, canine and human osteosarcoma cell lines and patient derived material. Higher levels of ALDH expression correlated with metastatic disease, intracellular copper showed the opposite trend, with higher levels associated with primary tumours. The copper chelator disulfiram, also a repurposing candidate in glioblastoma and other cancers, showed selective cytotoxicity to osteosarcoma cells, an effect that was increased with the addition

of copper dichloride. *In vitro* treatment with the combination of low dose doxorubicin, disulfiram and copper dichloride was effective in targeting human osteosarcoma cells. Validation in a suitable animal model, for example canines, is urgently required to follow these results up.

Nicotinamide (niacin) supplement increases lipid metabolism and ROS-induced energy disruption in triple-negative breast cancer: potential for drug repositioning as an anti-tumor agent

Published in Molecular Oncology

Nicotinamide (vitamin B3) is emerging as an increasingly interesting repurposing candidate in a number of different malignancies. In this work nicotinamide has been shown to target triple negative breast cancer (TNBC) cells. Using multi-omics analysis showed that it decreased mitochondrial membrane potential and ATP production, increased the activities of reverse electron transport (RET), fatty acid β-oxidation other metabolic pathways in TNBC. These metabolic alterations resulting in an increased reactive oxygen species (ROS) generation. The increased ROS levels triggered apoptosis and suppressed tumour growth and metastasis of TNBC in both human organoids and xenograft mouse models. Metabolic plasticity is a hallmark of cancer, and this finding suggests that nicotinamide might be effective at targeting TNBC cells.