Latest news about drug repurposing in oncology #13

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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

The allergy mediator histamine confers resistance to immunotherapy in cancer patients via activation of the macrophage histamine receptor H1

Published in Cancer Cell

Beginning with the finding that cancer patients treated with immune checkpoint inhibitors and co-medicating with antihistamines had better outcomes than non-antihistamine-treated patients, this *in vitro* and *in vivo* study explores the relationship between histamine and immuno-suppression. A key finding is that histamine and histamine receptor H1 (HRH1) are frequently increased in the tumour microenvironment and can induce T cell dysfunction via interaction with macrophage HRH1. Significantly, animal models treated with the antihistamine fexofenadine and checkpoint inhibitors showed improved survival compared to mice treated with either drug alone.

Clinical data

Clinical trials

Phase 2 trial of monoamine oxidase inhibitor phenelzine in biochemical recurrent prostate cancer
Published in Prostate Cancer and Prostatic Diseases
Results from a small (n=20) Phase II single arm study phenelzine in patients with biochemical recurrence of castrate-sensitive prostate cancer. The intervention was phenelzine 30 mg orally twice daily and the primary endpoint was the proportion of patients who achieved a PSA decline of ≥50% from baseline. A ≥ 50% PSA decline was reported in 10% of subjects. Eleven of 20 patients (55%) had measurable PSA decline compared to baseline with the greatest decline being 74%. Tolerability was good, and patients also reported a reduction in anxiety, although there was no change in depressive symptoms.

Levetiracetam as a sensitizer of concurrent chemoradiotherapy in newly diagnosed glioblastoma: An open-label phase 2 study
Published in Cancer Medicine
In this multi-centre single-arm Korean phase 2 trial, glioblastoma patients scheduled for surgical resection received the anti-epileptic drug levetiracetam starting before surgery and continued until the end of adjuvant temozolomide. The addition of levetiracetam was well tolerated. Neither progression-free survival (PFS) nor overall survival was different from those of historical controls. Subgroups analyses indicated a possible association of levetiracetam use and PFS in patients with unmethylated MGMT tumours and in patients less than 65 years.

Observational studies

Outcomes of women treated with progestin and metformin for atypical endometrial hyperplasia and early endometrial cancer: a systematic review and meta-analysis
Published in International Journal of Gynecological Cancer
This is a PRISMA meta-analysis of disease relapse after progestin and metformin versus progestin therapy alone in patients with endometrial hyperplasia or cancer. Six studies, two RCTs and four retrospective trials were included with 621 patients in total. The key finding is that women who receive progestin and metformin therapy have lower disease relapse than those receiving progestin alone. Combined therapy was not associated with significantly different remission rates or with different pregnancy and live birth rates.

Preclinical data

Synergistic Anti-Tumor Effect of Simvastatin Combined to Chemotherapy in Osteosarcoma
Published in Cancers
In this in pre-clinical study simvastatin is shown to enhance the effects of a range of chemotherapeutic drugs commonly used against osteosarcoma. *In vitro* simvastatin showed synergy with cisplatin, ifosfamide, etoposide, doxorubicin and vincristine but not methotrexate. *In vivo* the addition of simvastatin increased the effect of doxorubicin on reducing primary tumour growth and in reducing metastatic spread. This study supports the clinical investigation of the addition of a statin to standard chemotherapy regimens for primary osteosarcoma.

EZH2 presents a therapeutic target for neuroendocrine tumors of the small intestine
Published in Scientific Reports
EZH2 is a target of interest in multiple cancer types and small molecule inhibitors are currently being tested in early phase trials. The study shows that EZH2 is highly expressed in small intestinal neuroendocrine tumours (SI-NETs), both in primary tumour samples and metastases. Two targeted agents - CPI-1205 and GSK126 - reduced cell viability and induced apoptosis in SI-NET cell lines. Metformin, alone and in combination with the targeted agents, also reduced EZH2 expression and reduced viability in the cell lines. This is a second group that has shown that metformin targets EZH2.

The Antibiotic Drug Trimethoprim Suppresses Tumor Growth and Metastasis via Targeting Snail
Published in British Journal of Pharmacology
SNAI1 (Snail) is a transcription factor that is upregulated in many cancers and is associated with poor outcomes, it is also widely considered undruggable. This study identified the antibiotic trimethoprim as directly targeting Snail, suppressing acetylation and promoting Snail degredation. *In vivo* data showed that treatment with trimethoprim was active, particularly in reducing the incidence of metastasis in murine models of breast cancer (MMTV-PyMT and 4T1.2). Animal data also showed reduced growth of primary tumours in colorectal and breast cancer models.

[Patient-derived xenografts and in vitro model show rationale for imatinib mesylate repurposing in HEY1-NCoA2-driven mesenchymal chondrosarcoma]
Published in Laboratory Investigation
HEY1-NCoA2 gene fusion is a key driver of mesenchymal chondrosarcoma, a rare subtype that primarily affects younger patients. Previous work has shown that PDGFR signaling could be involved in MCS tumorigenesis, and in this study imatinib was used to treat patient-derived xenograft models of MCS harbouring the HEY1-NCoA2 gene fusion. In line with *in vitro* results, treatment of the PDX models showed that imatinib was able to significantly reduce tumour growth.

[TET2 as a tumor suppressor and therapeutic target in T-cell acute lymphoblastic leukemia]
Published in PNAS
Pediatric T-cell acute lymphoblastic leukemia (T-ALL) is an aggressive malignancy in need of novel therapies to prevent relapse and reduce treatment toxicity. This study reveals frequent (~88%) transcriptional silencing or repression of the tumour suppressor TET2 in T-ALL, correlated with hypermethylation of the TET2 promoter. Treatment with 5-azacytidine (5-aza) restores TET2 expression and increases apoptosis. Combination of 5-aza and acorbic acid showed synergy.

Other drug repurposing news

[A Database of Drug Repurposing Clinical Trials in Oncology]
Published in Frontiers in Pharmacology
The number of drug repurposing trials exploring the use of non-cancer drugs as anticancer agents has, to date, not been explored in detail. This paper, from the Anticancer Fund team, outlines the methodology for producing a database of active repurposing trials, and also a first analyse of this activity. In addition to highlighting a degree of duplication of trial activity, it also shows a wide range of drug candidates and cancers are being pursued.