Latest news about drug repurposing in oncology #9

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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

Repurposing Infectious Diseases Vaccines Against Cancer
Published in Frontiers in Oncology
A review of the potential for the repurposing of existing, licensed infectious diseases vaccines as anticancer agents by a team at the Anticancer Fund. The review finds that 16 such vaccines have potential, with 10 of them subject of clinical trials. A number of particularly promising findings that warrant further clinical investigation are also highlighted.

Clinical data

Clinical trials

Repurposing metformin as anticancer drug: Randomized controlled trial in advanced prostate cancer (MANSMED)
Published in Urologic Oncology
A randomised controlled trial (n=124) of metformin with standard of care in hormone sensitive prostate cancer, with a primary end-point of castration-resistant prostate cancer-free survival. With a median follow up of 22 months, the end-point was significantly improved with metformin (29 months, 95% CI 25-33 vs. 20 months 95% CI 16-24; P = 0.01). Subgroup analysis showed benefit particularly with high-risk localised disease or low tumour volume metastatic disease. However, the trial included heterogenous patient populations with different standard of care treatments.

Vitamin D Supplementation and Disease-Free Survival in Stage II Melanoma: A Randomized Placebo Controlled Trial
Published in Nutrients.
A randomised controlled trial (n =104) of vitamin D3 in newly resected stage II melanoma patients with a primary end-point of a reduction in the rate of recurrence. The intervention was 3-years of vitamin D3 (100,000 IU every 50 days) vs placebo. After a median follow-up of 3 years, no difference by treatment in disease-free survival was observed. The trial was however terminated early for accrual issues and therefore underpowered to definitely answer the question unfortunately.

Observational studies

Effect of perioperative flurbiprofen axetil on long-term survival of patients with esophageal carcinoma who underwent thoracoscopic esophagectomy: A retrospective study
Journal of Surgical Oncology
A retrospective study assessing the impact of perioperative flurbiprofen axetil (an NSAID) on recurrence-free and overall survival in esophageal carcinoma patients undergoing thoracoscopic esophagectomy. The data, for 847 eligible patients from a single institution, shows an improved RFS and OS in the NSAID groups vs. the non-NSAID group. As usual there are caveats regarding the use of retrospective data but this study is strongly supportive of a prospective randomised trial in this high-need population.

Intraoperative opioid exposure, tumour genomic alterations, and survival differences in people with lung adenocarcinoma
Published in British Journal of Anaesthesia
Addresses the question of the effects of perioperative analgesics on long-term outcomes, in this case in early stage non-small cell lung cancer. In particular the use of ketamine rather than opioids was associated with improved recurrence-free survival. Also interesting is the analysis of genomic interactions between survival pathways and opioids in patient samples.

Beta-adrenergic receptor blockers and liver cancer mortality in a national cohort of hepatocellular carcinoma patients
Published in Scandinavian Journal of Gastroenterology
A retrospective study (n=2104) based on the Swedish Cancer Registry exploring the association between use of beta-blockers and liver cancer outcomes. Compared with non-use, beta-blocker use at cancer diagnosis was associated with lower liver cancer mortality [0.82 (0.72–0.94); p = .005]. Statistically significant associations were observed for non-selective [0.71 (0.55–0.91); p = .006], b1-receptor selective
[0.86 [0.75–1.00); p = .049] and lipophilic [0.78 (0.67–0.90); p = .001] b-blockers. Cox proportional hazards regression analysis for an association between types of antihypertensive medication (e.g. ACEi, ARBs, CCB etc) showed a significant (p=.03) association only for selective beta-blockers.

Case reports

Itraconazole-A New Player in the Therapy of Advanced Basal Cell Carcinoma: A Case Report
Published in JCO Oncology Practice
A case report of a patient with advanced basal cell carcinoma who showed extended clinical benefit from itraconazole after prior vismodegib treatment.

Preclinical data

Inhibition of Polyamine Biosynthesis Using Difluoromethylornithine Acts as a Potent Immune Modulator and Displays Therapeutic Synergy With PD-1-blockade
Published in Journal of Immunotherapy
In this study DFMO was used with anti-PD1 check-point inhibition in murine models known to be susceptible and resistant to check-point inhibitors (LLC-A9F1 or B16/F10 cell lines). DFMO enhanced PD-1 blockade in both partially checkpoint-responsive and refractory tumours. Analysis showed that the combination therapy increased the survival and activity of intratumoural CD8+ T

cells. Improving the response rate of checkpoint inhibitors is a major clinical challenge and this early work warrants further investigation.

Targeting polyamine as a novel therapy in xenograft models of malignant pleural mesothelioma
Published in Lung Cancer
In this in vivo study DFMO is shown to reduce tumour growth and increase survival in two models of malignant pleural mesothelioma - a cancer with very high unmet needs. DFMO treatment was associated with spermidine depletion, and the anti-tumour effects were reversed by exogenous spermidine. The treatment was shown to be non-toxic and the doses of drug used were within the range used clinically in humans - though drug was supplied ad libitum in water rather than directly administered.

Maprotiline Suppresses Cholesterol Biosynthesis and Hepatocellular Carcinoma Progression Through Direct Targeting of CRABP1
Published in Frontiers in Pharmacology
An in vitro/in vivo study exploring the effect of the antidepressant maprotiline on two hepatocarcinoma cell lines (Huh7 and HepG2). In vitro maprotiline reduced proliferation, invasion and increased apoptosis and synergised with sorafenib. Mechanistically the effects are associated with reduce cholesterol biosynthesis via the MAPK/ERK pathway. In vivo data shows reduced tumour growth and low toxicity versus controls.