Latest news about drug repurposing in oncology #10

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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

A phase Ib/IIa trial of 9 repurposed drugs combined with temozolomide for the treatment of recurrent glioblastoma: CUSP9v3
Published in Neuro-Oncology Advances
The CUSP9v3 combines nine repurposed non-cancer drugs with metronomic temozolomide for patients with recurrent glioblastoma. This drug combination is rationally designed to target multiple escape mechanisms by which refractory disease evades treatment. Such a complex cocktail of drugs is challenging to implement and it raises safety concerns. This trial report shows that the treatment can be administered safely and there is an encouraging efficacy signal. The report also discusses the prospect of a randomised Phase II trial to further assess efficacy.

Clinical data

Clinical trials

Perioperative analgesia with parecoxib sodium improves postoperative pain and immune function in patients undergoing hepatectomy for hepatocellular carcinoma
Published in Journal of Evaluation in Clinical Practice
This small (n=80) randomised trial in HCC showed that perioperative parecoxib + fentanyl had improved analgesic effects compared to fentanyl alone, and was associated with improved DFS (median of 19 months vs 14 months, $P < 0.05$).

Forging a Path forMetformin Use in Inoperable Locally Advanced Non–Small Cell Lung Cancer
Published in JAMA Oncology
Results of two small metformin trials in non-diabetic patients with locally advanced NSCLC, both published in this same issue of JAMA Oncology, are discussed in this editorial. In the OCOG-ALMERA, (n=54), trial of metformin combined with chemoradiotherapy the metformin arm had reduced efficacy and increased toxicity compared to chemoradiation alone. In the NRG-LU001 trial, (n=170), there were no significant differences in PFS, OS or adverse event rates. The editorial outlines the main details of these two studies and discusses the role metformin might play in NSCLC in the era of onco-immunology.

Effect of Celecoxib vs Placebo as Adjuvant Therapy on Disease-Free Survival Among Patients With Breast Cancer: The REACT Randomized Clinical Trial
Published in JAMA Oncology
This large (n=2639) trial of adjuvant celecoxib vs. placebo in women with HER2-negative primary breast cancer finds no effect on disease free survival at 10-years follow up. Patients received celecoxib, 400 mg, or placebo, once daily for 2 years. Analysis at 10 years shows no difference in outcomes between celecoxib or placebo arms, sub-group analysis of ER+ and ER- patients also showed no differences.

Cancer Antigen 15-3/Mucin 1 Levels in CCTG MA.32: A Breast Cancer Randomized Trial of Metformin vs Placebo
Published in JNCI Cancer Spectrum
Confirmation from a randomised placebo controlled trial that metformin reduces circulating levels of the tumour marker CA 15–3 by approximately 6%. While confirming a previous observation study data is not yet mature enough to assess whether there is a clinically relevant impact.

Observational studies

Association of statin use with clinical outcomes in patients with triple-negative breast cancer
Published in Cancer
In this retrospective study, using SEER data, statin use initiated in the 12 months after breast cancer diagnosis was associated with improved OS and breast cancer-specific survival in women with TNBC but not other forms of breast cancer. The study included women aged ≥ 66 years who had stage I, II, and III breast cancer and included 1534 women with TBNC, for whom the HR for overall survival was 0.70 (95% CI, 0.50- 0.99; P = .046).

Repurposed floxacins targeting RSK4 prevent chemoresistance and metastasis in lung and bladder cancer
Published in Science Translational Medicine
A drug screen identifies floxacin antibiotics as inhibitors of RSK4, a kinase which is associated with drug resistance and metastasis. *In vitro* and *in vivo* experiments show that floxacin antibiotics inhibit RSK4 and can reproduce the effects of genetic silencing of the kinase, including inhibition of cell migration and invasion. Supporting data for a clinical effect is shown in an analysis of data from a phase 3 RCT where prophylactic levofloxacin was associated with improved outcomes median (median OS of 72 vs. 59 months, HR 0.83; 95% CI 0.69-0.999).

Case reports

Activation of the integrated stress response confers vulnerability to mitoribosome-targeting antibiotics in melanoma
Published in JEM (Journal of Experimental Medicine)
Targeting the integrated stress response in treatment-resistant melanoma cell lines and models, the authors investigate the effects of doxycycline and tigecycline on drug-tolerant persister cells. It is shown that ISR-dependent survival also relies on up-regulation of mitochondrial protein synthesis, a vulnerability that can be exploited using mitoribosome-targeting antibiotics. The analysis includes combinations of antibiotics with standard targeted melanoma agents. Finally, a case report of a refractory metastatic melanoma patient treated with doxycycline is also reported.

Preclinical data

Mebendazole disrupts stromal desmoplasia and tumorigenesis in two models of pancreatic cancer
Published in Oncotarget
In vivo study showing that mebendazole reduced pancreatic cancer incidence, tumour progression and metastatic spread. In the KPC model both early and late treatment with mebendazole reduced tumour incidence.

D-Propranolol Impairs EGFR Trafficking and Destabilizes Mutant p53 Counteracting AKT Signaling and Tumor Malignancy
Published in Cancers
In this *in vivo* study the D-enantiomer of propranolol is shown to destabilise gain-of-function mutant p53 and reduce levels of cell-surface FGFR. In a mouse model of aggressive gastric cancer daily propranolol reduced tumour growth and increased survival. Given the clinical importance of EGFR and mutant p53 in multiple tumour types this finding adds to the rationale for clinical investigation of propranolol.

Potential and mechanism of mebendazole for treatment and maintenance of ovarian cancer
Published in Gynecologic Oncology
The authors explore the effects of mebendazole using cisplatin-resistant PDX models of high grade serous ovarian cancer and a range of ovarian cancer cell lines differing in p53 status. They show that mebendazole inhibits ovarian cancer tumour growth at low nanomolar concentration and at physiologically relevant doses. Furthermore, mebendazole is synergistic with the mutant p53-targeted agent PRIMA-MET.

Itraconazole Exerts its Anti-Tumor Effect in Esophageal Cancer by Suppressing the HER2/AKT Signaling Pathway
Published in Molecular Cancer Therapeutics
Using *in vitro*, *in vivo* and human data from a clinical trial (NCT02749513) - the authors show that itraconazole targets the HER2-AKT axis, in esophageal cancer. *In vivo* experiments showed a reduction in growth of flank-implanted tumours. Data from patients in the clinical trial showed decreased HER2 total protein expression and phosphorylation of AKT and S6 proteins in tumours.