Latest news about drug repurposing in oncology #7

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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

Effect of Celecoxib vs Placebo Added to Standard Adjuvant Therapy on Disease-Free Survival Among Patients With Stage III Colon Cancer
Published in JAMA
This article reports the celecoxib comparison of the US CALGB/SWOG 80702 colorectal adjuvant trial. Patients received either celecoxib (400 mg) or placebo for 3 years. No difference was found in terms of DFS (HR 0.89; 95%CI, 0.76-1.03) or OS (0.86; 95%CI, 0.72-1.04). Though the DFS curves clearly separate after 2 years in favour of the celecoxib arm, this difference is not significant, meaning that, if there is any effect, it is very modest.

Clinical data

Clinical trials

A phase 2a clinical study on the safety and efficacy of individualized dosed mebendazole in patients with advanced gastrointestinal cancer
Published in Scientific Reports
In this small Swedish trial in patients with advanced GI cancers, mebendazole, an anti-parasitic drug, was given at high doses (up to 4g per day). The trial was terminated early for lack of efficacy. Of the 8 evaluable patients, all had progressive disease at the first assessment at 8 weeks. 4 patients experienced hyper-progressive disease during treatment, though a causal relationship cannot be established nor ruled out. The drug was well tolerated but few patients reached the target plasma concentration. In conclusion, single drug individualized dosed mebendazole had no anti-cancer effect in patients with progressive refractory gastrointestinal cancer.

Aprepitant for Cough in Lung Cancer. A Randomized Placebo-controlled Trial and Mechanistic Insights
Published in American Journal of Respiratory and Critical Care Medicine
In this British randomised double-blind crossover trial of 20 lung cancer patients with bothersome cough, a 3-day treatment with aprepitant, a neurokinin-1 antagonist approved for chemotherapy-induced nausea and vomiting, improved cough endpoints (frequency and severity) and patient-reported outcomes. Cough was measured with acoustic cough monitoring. A 30% frequency reduction was noted over a 24-hour period compared to placebo. In the same article, preclinical mechanistic experiments suggest an inhibition of peripheral vagal nerves by aprepitant. These results confirm results from a larger pragmatic randomized trial conducted in India and reported last year (https://pubmed.ncbi.nlm.nih.gov/31958446/).

Observational studies

Postdiagnosis aspirin use associated with decreased biliary tract cancer-specific mortality in a large nationwide cohort
Published in Hepatology
In this nation-wide Taiwanese observational study, Liao et al report a positive association between post-diagnosis aspirin use and survival in patients with biliary tract cancers. For cancer-specific deaths, the multivariate HR for postdiagnosis aspirin users was 0.55 (95% CI, 0.51 to 0.58) as compared with non-users. This association was observed for all biliary tract cancer subtypes. Specific methods used to account for competing risks for

cardiovascular deaths and for immortal-time bias confirmed this positive association.

Case reports

Overcoming acquired resistance to PD-1 inhibitor with the addition of metformin in small cell lung cancer (SCLC)
Published in Cancer Immunology, Immunotherapy
This SCLC patient who developed new lesions after an initial response to nivolumab experienced a partial response following the introduction of metformin to her treatment. 6 months later, at the time of the report the disease is stable. This is the second case reported by this team - the first was a NSCLC patient - who are now conducting a single-arm phase 2 trial (NCT03048500) testing the addition of metformin to nivolumab in NSCLC.

Preclinical data

Aspirin reduces the incidence of metastasis in a pre-clinical study of Braf mutant serrated colorectal neoplasia
Published in British Journal of Cancer
Though this one may be seen as 'another' preclinical paper about aspirin and colorectal cancer, the model they used is known to successfully recapitulate the progression of serrated colorectal neoplasia in humans. They show that aspirin does not reduce the incidence of BRAF-mutant colorectal cancers in this mouse model but reduce the incidence of metastasis. Their work also suggest CRC molecular subtypes that may benefit from aspirin treatment.

The disulfiram/copper complex induces apoptosis and inhibits tumor growth in human osteosarcoma by activating the ROS/JNK signaling pathway
Published in The Journal of Biochemistry
In a xenograft model of osteosarcoma, Guo et al shows that disulfiram with copper could slow down tumour growth at doses compatible with human use. They suggest this is achieved through induction of apoptosis of osteosarcoma cells via by activation of the ROS/JNK signalling pathway.

Targeting MerTK Enhances Adaptive Immune Responses After Radiation Therapy
Published in Intl Journal of Radiation Oncology – Biology - Physics
In a series of mice experiment in Panc02 and CT26 models, this teams shows that MerTK, a member of the Tyro3-Axl-MerTK family of receptor tyrosine kinase, inhibits tumour control by radiation and negatively regulates immune priming by radiation. They then show that the anticoagulant warfarin, known to inhibit MerTK and Axl, improves tumour control with radiation therapy and

promotes adaptive immune-mediated local and abscopal tumour control after radiation therapy. Finally, using a cohort of NSCLC patients treated with stereotactic body radiation therapy, they report a positive association between warfarin use at the time of treatment and PFS. No association was found for OS.

Sulindac modulates the response of proficient MMR colorectal cancer to anti-PD-L1 immunotherapy
Published in Molecular Cancer Therapeutics
Sulindac - a non-steroidal anti-inflammatory drug - is able to make proficient mismatch repair CRC tumours sensitive to anti-PD-1 treatment in this series of preclinical experiments. This is mediated by CD8+ T-cells infiltration and reduction of PD-L1 expression in both tumours and tumour-derived exosomes. The dose used is equivalent to less than a quarter of the human recommended dose. At this dose, plasma PGE2 levels were not modified by sulindac.

N-acetyl cysteine induces quiescent-like pancreatic stellate cells from an active state and attenuates cancer-stroma interactions
Published in Journal of Experimental & Clinical Cancer Research
Feng et al explore tumour-stroma interactions in pancreatic ductal adenocarcinoma models. They show that the approved antioxidant n-acetyl-cysteine suppresses pro-tumoural effects of pancreatic stellate cells. The combination of n-acetyl-cysteine with the antidiabetic drug pioglitazone maintained stellate cells in a quiescent state. The combination was effective in vivo in 2 different models. It was even superior to gemcitabine. Whether the combination works in models that recapitulate better the stromal heterogeneity in human pancreatic cancer remains an open question.

De novo purine biosynthesis is a major driver of chemoresistance in glioblastoma
Published in Brain
Shireman et al show that glioblastoma cells epigenetically upregulate a protein called ARL13B to adapt to temozolomide chemotherapy. ARL13B interacts with an enzyme called IMPDH2, resulting in an increased de novo purine synthesis to meet glioblastoma cells nucleotide needs. They successfully used mycophenolate mofetil, approved to prevent graft rejection in transplanted patients, and a known IMPDH2 inhibitor to prevent this phenomenon. At a dose compatible with the approved human dose, mycophenolate mofetil with temozolomide prolonged mice survival in 3 different models representing the main glioblastoma subtypes.

Improved Radium-223 Therapy with Combination Epithelial Sodium Channel Blockade
Published in The Journal of Nuclear Medicine

In this series of mice experiments, Abou et al reports beneficial effects of combining amiloride, a diuretic drug blocking epithelial sodium ion channels, with the radio-isotope Radium-223 dichloride. In their model, amiloride shifted the uptake pattern of Radium-223 in beneficial ways, with a lower uptake in the gut – reducing GI toxicity - and an almost doubling of bone uptake – enhancing anticancer activity. Synergism was confirmed in 2 xenograft models (1 bone-metastases prostate cancer and 1 osteosarcoma) with better tolerability and greater tumour inhibition with the combination.

Repositioning metformin and propranolol for colorectal and triple negative breast cancers treatment
Published in Scientific Reports
In CRC and TNBC mice models, Anselmino et al look at the combination of the antidiabetic drug metformin with the antihypertensive drug propranolol, using doses compatible with their human equivalent doses. Remarkably, the combination is able to prevent resistance to 5-FU in a CRC model. The combination is also to reduce both tumour growth and metastases formation in TNBC and CRC model suggesting the combination could be of interest in the (neo-)adjuvant setting.

The white matter is a pro-differentiative niche for glioblastoma
Published in Nature Communications
Brooks et al provide evidence that glioblastoma cells with oligodendrocyte lineage competency can acquire pre-oligodendrocyte fate when in contact with white matter. This tumour cell differentiation is driven by selective white matter upregulation of SOX10 which is involved in oligodendrogenesis.
They successfully used an asthma drug approved in Japan, pranlukast (that belongs to the same class as the broadly available montelukast) to upregulate SOX10. Besides its main asthma target, pranlukast inhibits GPR17, a negative regulator of oligodendrocyte development. Treatment
with pranlukast increased differentiation to pre-oligodendrocyte cells in a SOX10 dependent manner. In vivo experiments used intrathecal injection
since pranlukast has poor CNS penetration. Tumours with oligodendrocyte lineage competency are the best GBM subtypes for a potential clinical translation of these findings.