Latest news about drug repurposing in oncology #19

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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 context.

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

Top stories

A reversible SRC-relayed COX2 inflammatory program drives resistance to BRAF and EGFR inhibition in BRAFV600E colorectal tumors

Published in Nature Cancer

BRAFV600E mutation is associated with a poor prognosis in metastatic colorectal cancer (mCRC), despite the use of targeted therapies shown to be effective in similarly mutated melanoma. In seeking to understand the difference in response in mCRC, the authors uncover an interplay between oncogenic pathways, and that drug targeting of BRAF ± EGFR causes a compensatory activation of SRC kinases leading to treatment resistance. Intriguingly the authors explore this mechanism and find that prostaglandin E2 (PGE2) mediates this pathway. COX2 inhibition, using celecoxib, reduces PGE2 and averts the resistance to BRAF treatment. Using patient-derived xenograft models the authors then show that the addition of celecoxib to standard of care targeted

therapies leads to improved survival and durable responses. These results clearly warrant clinical investigation. It also shows that analysis of resistance mechanisms means that current treatments can be made effective again with the addition of other drugs, including non-cancer drugs like celecoxib.

Clinical data

Clinical trials

Beneficial Effects of Mifepristone Treatment in Patients with Breast Cancer Selected by the Progesterone Receptor Isoform Ratio: Results from the MIPRA Trial
Published in Clinical Cancer Research
In this window of opportunity trial, women with luminal breast cancer and progesterone receptor isoform A (PRA) > isoform B (PRB), were treated with 14 days of mifepristone prior to surgical resection. Results showed that the treatment was associated with a statistically significant reduction in Ki67 staining. There were also an increase in tumour-inflitrating lymphocytes and a decrease in hormone receptor expression. While these and other biomarker and proteomic analyses are positive further studies are required to assess the clinical impact and role that mifepristone treatment could have in breast cancer.

Metformin increases natural killer cell functions in head and neck squamous cell carcinoma through CXCL1 inhibition
Published in Journal for Immunotherapy of Cancer
This paper reports on analyses from two window of opportunity trials in head and neck squamous cell carcinoma (HNSCC) patients treated with metformin for two weeks prior to surgical resection and chemo-radiotherapy. Data shows that metformin treatment was associated with an increase in natural killer (NK) cell numbers and, via the CXCL1 pathway, an increase in NK cell cytotoxicity against HNSCC cells. Given that lower NK cells numbers are correlated with worse outcomes in HNSCC patients, these effects of metformin may lead to clinically meaningful changes. However, prospective randomised trials are required to assess this possibility.

Neoadjuvant docetaxel, epirubicin, and cyclophosphamide with or without metformin in breast cancer patients with metabolic abnormality: results from the randomized Phase II NeoMET trial
Published in Breast Cancer Research and Treatment
In this trial, breast cancer patients with metabolic syndrome were randomised to neoadjuvant paclitaxel, epirubicin and cyclophosphamide with or without metformin. The primary end point was total pathological complete response. Results showed no significant difference between the two arms, although the

metformin arm showed favourable changes in metabolic parameters. Secondary analyses looked at disease-free and overall survival, finding no differences between arms - suggesting no influence on disease progression of metformin in this patient population.

Vitamin C boosts DNA demethylation in *TET2* germline mutation carriers
Published in Clinical Epigenetics
This interesting study looked at a single family harbouring a germline mutation in the TET2 that is associated with lymphoma. Investigators assessed the impact of oral ascorbic acid (vitamin C) on TET2 demethylation in study participants in a year-long trial. Affected family members (2 who had suffered from lymphoma, 3 affected but no lymphoma and 3 non-carriers) were tested at baseline, 6- and 12-months and assessed for DNA methylation by analyzing genome-wide DNA methylation and gene expression patterns. Results showed that oral vitamin C induced reductions in the proportion of hypermethylated loci and diminished gene expression differences between TET2 mutation carriers and controls. As TET2 germline mutations appear to predispose to haematological malignancies, the impact of this low-cost and non-toxic intervention warrants further clinical investigation.

Case reports

Biomodulatory therapy induces durable remissions in multi-system Langerhans cell histiocytosis
Published in Leukemia and Lymphoma
Refractory multi-system Langerhans cell histiocytosis is a rare neoplastic condition normally treated with chemotherapy drugs that have high rates of toxicity associated with them. For patients who cannot be treated with these drugs there are few options available. In this case series of 11 patients, including two infants, a metronomic cocktail of low-dose trofosfamide, the anti-diabetic drug pioglitazone, low-dose dexamethasone and the NSAID etoricoxib (together termed a metronomic biomodularity therapy), was used as a treatment on a compassionate use basis. Of the 11, four patients (including two heavily pre-treated pediatric patients) achieved complete remissions, three patients experienced partial remission and four had stable disease. Quite rightly the authors conclude that these positive results support a prospective clinical trial.

Preclinical data

Reversal of cancer gene expression identifies repurposed drugs for diffuse intrinsic pontine glioma
Published in Acta Neuropathologica Communications
Bioinformatics pipelines are an increasingly important tool in the drug

repurposing armoury. In this paper a pipeline was used to search for drug candidates for diffuse intrinsic pontine glioma (DIPG) - a disease that has only palliative treatments at the moment. Using a range of algorithms and techniques the authors identify triptolide, mycophenolic acid and mycophenolate mofetil (MMF) as candidates for repurposing - with their in silico work validated i*n vitro* and *in vivo*. While treatment with MMF in particular showed improved survival in an orthotopic model, the drug was used at a high dose that is likely to be toxic in children. This means that techniques such as convection-enhanced delivery may be required to deliver the drug at the right dose without causing systemic toxicity.

Chloroquine Combined With Rapamycin Arrests Tumor Growth in a Patient-derived Orthotopic Xenograft (PDOX) Mouse Model of Dedifferentiated Liposarcoma

Published in In Vivo

Dedifferentiated liposarcoma is a neglected cancer in need of new treatment options. This *in vivo* study tested sirolimus and chloroquine in a patient-derived orthotopic xenograft mouse model from a lab that has a proven track record with such models. The study looked at sirolimus and chloroquine as single agents and as a combination in comparison to untreated controls. Whereas single agent chloroquine showed almost no activity, sirolimus alone was active in reducing tumour volume. The combination was very synergistic - as confirmed also when looking at the apoptotic cell count. The data in this animal model certainly looks promising and in need of confirmation, it also clearly suggests that an early phase trial in humans should be developed.

Repurposing live attenuated trivalent MMR vaccine as cost-effective cancer immunotherapy

Published in Frontiers in Oncology

An interesting pre-clinical study that uses low-doses of measles, mumps, rubella (MMR) vaccine as an intra-tumoural injection in liver and colorectal cancers in animal models. The results suggest that the vaccine has low levels of direct cytotoxicity but that it slows tumour growth through enhanced immune responses in the microenvironment of the tumour. A nice demonstration of a low-cost and widely accessible immunotherapy - it will be interesting to watch how this develops in the future.

Repurposing Ivermectin to augment chemotherapy's efficacy in osteosarcoma

Published in Human & Experimental Toxicology

Ivermectin is proving to be an interesting drug candidate in a range of different cancers, including in this study osteosarcoma. The authors investigate, *in vitro* and *in vivo*, the combination of ivermectin and doxorubicin - the standard of care drug that remains the backbone of osteosarcoma treatment worldwide.

Using a panel of cell lines they show that the combination of drugs is more effective than either drug alone in reducing cell viability. *In vivo* they show that ivermectin alone shows anti-osteosarcoma activity, reducing tumour volume compared to control but not as much as doxorubicin alone. But the combination shows synergy and the reduction in tumour volume is statistically significant compared to either drug alone. There is some analysis of mechanisms of action - primarily related to induced mitochondrial dysfunction and oxidative damage. The key question, of course, is where this work goes next.

Inhibitory effect of aspirin on inflammation-induced lung metastasis of cancer cells associated with neutrophil infiltration
Published in Surgery Today
The potential of perioperative therapies to reduce post-surgical distant metastasis remains under-explored in our opinion. This study combines animal data and retrospective human data to explore pulmonary metastasis - an issue of high clinical value in many cancers. In the animal model the LM8 osteosarcoma cell line - which is highly metastatic - is used to show that surgically induced lung injury is associated with higher rates of metastasis, and that perioperative aspirin can reduce that number. For the human data the authors compare patients with esophageal cancer patients who developed pneumonia post-surgery, and find that it is very strongly associated with lung metastasis - and that it correlates with CRP levels in patients. Both the animal data and the retrospective data are supportive of the idea that inflammatory tissue damage in the lungs is associated with pulmonary metastasis, and that aspirin or other anti-inflammatory may help reduce the risk.

Targeting tumor-stroma communication by blocking endothelin-1 receptors sensitizes high-grade serous ovarian cancer to PARP inhibition
Published in Cell Death and Disease
High-grade serous ovarian carcinoma (HG-SOC) is associated with a very high (~90%) rate of TP53 mutation - with drug resistance and late diagnosing together contributing to dismal outcomes for patients. This preclinical study explores the role of the tumour microenvironment in the emergence of resistance to PARP inhibition. The study shows that the endothelin-1/ET-1 receptor (ET-1/ET1R) axis restricts the DNA damage response to olaparib via interactions with the tumour, endothelial and activate fibroblastic cells. Treatment with macitentan, an endothelin receptor antagonist, in patient-derived xenografts synergises with olaparib to suppress metastatic progression and prolong survival, suggesting an active combination therapy to be explored further.

[Perioperative escape from dormancy of spontaneous micro-metastases: A role for malignant secretion of IL-6, IL-8, and VEGF, through adrenergic and prostaglandin signaling]

Published in Brain, Behaviour, and Immunity

Building on previous *in vivo* work that showed that minimally invasive surgical removal of tumours and their secreted factors was able to induce micro-metastases to enter a dormant state, this study further explores the mechanisms and whether perioperative drug treatment has any influence. Using the human breast cancer cell line MDA-MB-231HM orthotopically implanted in immune-deficient BALB/C nu/nu mice, the authors show that the addition of laporotomy to minimally invasive removal of the primary tumour induces escape from micro-metastatic dormancy. However, perioperative propranolol and etodolac reversed this shift induced by laporotomy. Mechanistically the authors show that the pro-metastatic effects are mediated by IL-6, IL-8, and VEGF - which are down-regulated by propranolol and etodolac treatment.