Latest news about drug repurposing in oncology #21

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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 story

Tumour immune rejection triggered by activation of α2-adrenergic receptors
Published in Nature
The race to find ways to improve the efficacy of immune checkpoint inhibitors is increasingly looking to non-cancer drugs as candidates. In this wide-ranging *in vivo* study, using multiple cancer cell lines and models, the authors show that alpha2 adrenergic agonists such as clonidine show single agent anti-cancer activity that is immune-related rather than directly cytotoxic. Tumours from treated mice contained increased infltrating T lymphocytes and reduced myeloid suppressor cell populations. These results provide a strong rationale for clinical investigation, both as single agents and in combination with checkpoint inhibition.

Clinical data

Clinical trials

A Randomized Phase II Study of Irinotecan Plus Cisplatin with or without Simvastatin in Ever-Smokers with Extended Disease Small Cell Lung Cancer
Published in Cancer Research and Treatment
This randomised open-label Phase II trial looked at the impact of simvastatin on ever-smokers with extended disease small cell lung cancer, with the 1-year survival rate as the primary end-point. The results show that the addition of simvastatin had no discernable impact on survival, nor on the rate of adverse events. One notable finding was that baseline hypertriglyceridemia was associated with improved survival and may be a prognostic factor.

A phase I trial of riluzole and sorafenib in patients with advanced solid tumors: CTEP #8850
Published in Clinical Trial
The combination of riluzole and sorafenib has been shown to synergistically inhibit BRAF wildtype and mutant GRM1 positive cell lines, both *in vitro* and in mouse xenograft models of melanoma. In this small dose-finding trial, 35 heavily-pretreated patients with advanced solid tumours, (around half with melanoma or colorectal cancer), were treated with the combination at four-dose levels. The maximum tolerated dose was found to be riluzole: 100 mg PO BID; sorafenib: 400 mg AM/200 mg PM. Best response was partial response in one patient, and stable disease in 11 (36%) patients.

Phase I / II trial of metformin as a chemo-radiosensitizer in a head and neck cancer patient population
Published in Oral Oncology
This small Phase I/II sought to assess the impact of metformin as a chemo-radiosensitiser in head and neck squamous cell carcinoma. However, the trial did not complete accrual, in part due to covid, and the resulting analysis is complicated by different subsets of patients and a lack of power. Unfortunately this outcome is likely to be repeated as the impacts of the pandemic become apparent on many of the small academic repurposing trials which have been quite common in recent years.

Effect of Vitamin D Supplements on Relapse or Death in a p53-Immunoreactive Subgroup With Digestive Tract Cancer
Published in Jama Network Open
In this retrospective study, data from the AMATERASU trial of post-operative vitamin D3 in digestive tract cancers was used to assess the impact of vitamin D3 supplementation (2000 IU/day) on 5-year recurrence free survival or death

based on p53-immunoreactivity. p53-immunoreactivity is associated with mutant p53 and was measured in serum and IHC. In contrast to the negative results from the original trial, this study found that patients in the immuno-reactive subset taking vitamin D3 showed significantly better survival compared to the immuno-reactive subset on placebo (hazard ratio [HR], 0.27; 95% CI, 0.11-0.61; P = .002). Though a post-hoc subgroup analysis, this is a striking finding that urgently needs testing prospectively. Replication in other cancer types should also be investigated, particularly in cancers where TP53 mutation is highly prevalent.

Observational trials

Efficacy and adverse events of anthracycline and propranolol combination in five dogs with stage 3 hemangiosarcoma
Published in Open Veterinary Journal
Canine hemangiosarcoma (HSA) is a relatively common cancer in dogs and has parallels with human angiosarcoma. In this retrospective study the authors assess the impact of the combination of propranolol and doxorubicin, a combination that has been of some interest in human angiosarcoma, on five dogs with stage 3 HSA. The authors report that of the 5 cases, four showed clinical benefit, including one complete response, one partial response and two stable disease. Adverse events were manageable and reversible. While retrospective and with only five cases, this study adds to the data in canine hemangiosarcoma and is of interest in angiosarcoma.

Preclinical data

Statins enhance the efficacy of HER2-targeting radioligand therapy in drug-resistant gastric cancers
Published in Proceedings Of The National Academy Of Sciences Of The United States Of America
Building on previous work that showed that statins can increase cell surface localisation of HER2, the authors exploit this finding to investigate whether it can lead to increased response to trastuzumab-based targeted radioligand therapy (RLT) . Using both *in vitro* and *in vivo* data, including patient derived xenografts, they show that the combination of lovastatin and RLT leads to inhibition of tumour growth and increased survival. Furthermore, the data also shows that there is a radio-protective effect when lovastatin is combined with RLT.

Targeting the mevalonate pathway suppresses ARID1A-inactivated cancers by promoting pyroptosis
Published in Cancer Cell
ARID1A, which functions as a tumour suppressor, is frequently inactivated in

more than 50% of ovarian clear cell carcinomas - a tumour type that has a bad prognosis. In this paper, Zhou and colleagues show that ARID1A inactivated cells undergo a form of cell death called pyroptosis when exposed to statins (which inhibits the mevalonate pathway). Since pyroptotic cell death induces the infiltration of CD8+ and CD4+ T cells, and ARID1A inactivation may make tumours sensitive to immune checkpoint inhibitors (ICI), the combination of simvastatin and ICI resulted in a strong anti-tumour effect in mice models including patient-derived xenografts. This is an impressive piece of research pinpointing how the consequences of ARID1A-inactivation may be exploited with a combination of 2 existing drugs.

Therapeutic potential of pentamidine for glioma-initiating cells and glioma cells through multimodal antitumor effects
Published in Cancer Science
Pentamidine is a broad spectrum anti-parasitic that has shown some evidence of anticancer activity, enough for it to be included in the ReDO database for example. In this preclinical study the authors screen a panel of drugs against a sample of glioma-initiating and glioblastoma cell lines and find that pentamidine emerged as the most potent candidate. Validation in a glioma KGS07 xenograft model recapitulated the *in vitro* results. The authors discuss the issue of CNS penetration of the drug, which has yet to be firmly established, but suggest that there is sufficient evidence to support clinical investigation of pentamidine in human gliomas.

Proteogenomic insights suggest druggable pathways in endometrial carcinoma
Published in Cancer Cell
This large, international study used a multi-omics approach to characterise a prospectively collected cohort of 130 endometrial carcinoma tumour samples and 20 normal controls. The proteogenomic analyses presented here suggest that an immune-related score may have utility to select patients for immune checkpoint inhibitor treatment. A second finding is that elevated MYC levels in non-diabetic patients may signal possible responders to metformin treatment. Finally, deep learning was used to develop an algorithm able to use classical histopathology images to identify molecular subtypes of endometrial cancer. Overall this is an impressive international collaborative effort and the metformin finding is of particular interest to the repurposing community.

Non-chemotherapy adjuvant agents in TP53 mutant Ewing sarcoma
Published in Scientific Reports
Refractory Ewing's sarcoma is a disease with a poor prognosis, therefore finding treatments that extend the duration of response to first-line multi-agent chemotherapy is a high unmet need. The authors of this study set out to test three agents - TK216, entinostat and enoxacin - in combination with etoposide *in*

vitro and *in vivo*. The *in vitro* studies included short-term and long-term exposure. In the mouse models engrafted mice were treated with etoposide followed by the tested drugs in order to simulate adjuvant treatment at human-equivalent doses. The results show that enoxacin, an FDA approved antibiotic, was able to slow tumour growth compared to untreated controls and compared to etoposide alone. These results suggest that enoxacin should be considered a candidate to add to multi-agent chemotherapy in first line Ewing's sarcoma treatment.