Latest news about drug repurposing in oncology #14

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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 stories

Improving the response to immune checkpoint inhibitors (ICI) - that is increasing the number of patients who positively respond to ICI treatment - would be a big win for oncology, and a major area of clinical research at the moment. Drug repurposing is one approach to doing this, the idea of adding a relatively non-toxic non-cancer drug and improving responses is an attractive option, particularly in those cancers where ICI treatment has been disappointing. There are three papers in this newsletter that reflect on this strategy. The first is a Danish paper by Fjæstad et al. They show that the anticancer effects of propranolol in mice models of fibrosarcoma and colorectal cancer are partly immune-mediated and that the effects are reduced in T-cell deficient mice. This was further tested using the combination of propranolol and anti-CTLA4 therapy - which improved the response rate compared to either agent alone.

In the paper by Deng and colleagues, the effects of glucocorticoid receptor (GR) signalling are investigated in pancreatic cancer models. The authors show that inhibiting GR signalling, including the use of mifepristone, downregulated PD-L1 and MHC-I and increased T-cell infiltration into tumours and overcomed resistance to ICI.
In the final paper, Luginbuhl et al report on a small clinical trial which assessed the combination of tadalafil, a PDE-5 inhibitor, and the ICI nivolumab in previously untreated head and neck squamous cell carcinoma patients. Patients (n=45) were randomised to four weeks of ICI or ICI + tadalfil prior to surgery, and were stratified by HBC status. Results show that tadalafil treatment was associated with changes in the immune milieu, for example a change in the CD8:CD4 ratio, but that there was no difference in outcomes between the treatment groups. The authors speculate that the duration of the intervention may have been too short and that a longer duration of treatment may be worth exploring in the future. Overall, this series of paper highlights the importance of putting these combinations to the clinical trial test, which would ideally be done in a multi-arm trial. We encourage anyone interested in selecting repurposed drugs for such a trial to connect with us.

Blockade of beta-adrenergic receptors reduces cancer growth and enhances the response to anti-CTLA4 therapy by modulating the tumor microenvironment
Published in Oncogene

Glucocorticoid receptor regulates PD-L1 and MHCI in pancreatic cancer cells to promote immune evasion and immunotherapy resistance
Published in Nature Communications

Tadalafil enhances immune signatures in response to neoadjuvant nivolumab in resectable head and neck squamous cell carcinoma
Published in Clinical Cancer Research

Clinical data

Clinical trials

A randomized phase 2 study of bicalutamide with or without metformin for biochemical recurrence in overweight or obese prostate cancer patients (BIMET-1)
Published in Prostate Cancer and Prostatic Diseases
In this small (n=29) open-label randomised trial of 8-weeks of metformin or observation prior to starting bicalutamide in non-diabetic men with biochemically recurrent prostate cancer, the primary objective was to evaluate the number of patients with undetectable PSA (< 0.2 ng/mL) at the end of 32

weeks. Immune correlatives were secondary, exploratory endpoints. While more patients in the metformin arm achieved modest reduction in PSA, there was no difference in the primary outcome in the two arms - leading to the trial ending early. Metformin monotherapy and metformin + bicalutamide was assorted with improved immunological indices (e.g. reduced PD-1+ NK cells).

BAMM (BRAF Autophagy and MEK Inhibition in Melanoma): A Phase I/II Trial of Dabrafenib, Trametinib, and Hydroxychloroquine in Advanced BRAFV600-mutant Melanoma

Published in Clinical Cancer Research

Autophagy is associated with resistance to BRAF/MEK inhibition in BRAFV600-mutant melanoma. In this multi-centre Phase I/II trial hydroxychloroquine was used to inhibit autophagy in combination with the targeted therapies dabrafenib and trametinib. For the Phase I the outcome was the recommended Phase II dose of hydroxychloroquine - which was 600 mg, twice daily. For the Phase II the primary outcome was to reach a one-year PFS rate of > 53%. The one-year PFS rate, (n=34 patients), was 48.2% [95% confidence interval (CI), 31.0%–65.5%], median PFS was 11.2 months (95% CI, 5.4–16.9 months), and response rate (RR) was 85% (95% CI, 64%–95%). In a hard to treat group of patients, (n=16), with high LDH the RR was 88% and median PFS and OS were 7.3 months and 22 months. While not reaching the specified primary outcome, the results in the LDH-high group are encouraging and a further trial in this population is now in progress.

Observational studies

Association of β-Blocker Use at Time of Radical Prostatectomy With Rate of Treatment for Prostate Cancer Recurrence

Published in Jama Network Open

This cohort study analysed prospectively collected data from four high-quality Norwegian registries to assess the impact on cancer recurrence of incidental use of non-selective beta blockers (nsBBs) in treatment-naive men undergoing radical prostatectomy. The main finding is that use of nsBBs at time of surgery was significantly associated with a lower risk of treatment for cancer recurrence (adjusted hazard ratio [aHR], 0.64; 95% CI, 0.42-0.96; P = .03). No such association was observed for use of selective beta blockers (aHR, 0.96; 95% CI, 0.84-1.11; P = .62). Subanalyses to correct for potential biases (i.e. including patients with early progression or healthier ECOG status) supported the main finding. The main nsBBs used by patients were carvedilol (56.9%) and propranolol (25.4%).

Case reports

[Pharmacological dose ascorbic acid administration in relapsed refractory multiple myeloma patients]
Published in Leukemia Research Reports
In this case series report in four relapsed recurrent multiple myeloma patients, pharmacological (IV) ascorbate was associated with clinical improvement. All patients were heavily pre-treated and progressive at the time of treatment. Pharmacological ascorbate (at a dose of 7.5 g infused over 30 minutes) was combined with carfilzomib-lenalidomide-dexamethasone (CRd) chemotherapy. At the end of four cycles of combined treatment, one patient showed complete remission and the other three patients very good partial remissions. Notably the four patients had previously been treated with two cycles of CRd and had shown no response. Further clinical studies of this combination are warranted.

Preclinical data

[Combination of Antiretroviral Drugs Zidovudine and Efavirenz Impairs Tumor Growths in a Mouse Model of Cancer]
Published in Viruses
Antiretroviral drugs are an intriguing class of repurposing candidates in oncology. Here two anti-HIV drugs, efavirenz and zidovudine, show *in vitro* and *in vivo* anticancer effects via inhibition of LINE1. Using a syngeneic mouse model, (C57/B16 mice injected subcutaneously with MC38 colorectal cancer cells), treatment with either drug, or the combination, reduced tumour volume compared to controls - with the combination being more effective than either treatment alone. Survival data is not reported but the treatment was well tolerated and the study supports further development of this approach, particularly the combination treatment.

[Rabeprazole has efficacy per se and reduces resistance to temozolomide in glioma via EMT inhibition]
Published in Cellular Oncology
Using patient derived cell cultures and a murine model, this paper outlines the effects of rabeprazole on glioma. In vitro rabeprazole reduced cell proliferation and migration and increased apoptosis - effects associated with a reduction in epithelial-mesenchymal transition (EMT). It was also shown to reverse resistance to temozolomide. *In vivo*, rabeprazole increased survival in a C6 rat glioma model, with data showing this was associated with a reduction in EMT (via STAT3 inhibition).

[ZIP9 Is a Druggable Determinant of Sex Differences in Melanoma]
Published in Cancer Research
In this elegant *in vitro* and *in vivo* study the authors identify a key factor associated with the poorer outcomes in males with melanoma. They show that testosterone is a driver of melanoma progression but that the effect is not mediated by androgen receptors, which are not highly expressed in melanoma, but via ZIP9 (a zinc transporter). Further the effects can be inhibited using classical anti-androgens, such as bicalutamide, as shown in two murine models. The study provides answers to a clinically relevant question and also support to the potential repurposing of anti-prostate cancer drugs for melanoma.

Other drug repurposing news

[Can Any Drug Be Repurposed for Cancer Treatment? A Systematic Assessment of the Scientific Literature]
Published in Cancers
This study reviews the literature for a range of non-cancer drugs to assess how many have published evidence of anticancer effects, and to report on the quality of the published papers showing those effects. Two panels of drugs are used - 100 from the most prescribed drugs, and 100 randomly selected drugs (with no overlaps between the two). The headline figure is that 69% have published evidence of anticancer effects, but based on the methodological assessment of the published papers the authors speculate that many of these are false-positives. This caution is warranted - and it is worth pointing out that for our own ReDO database there is an assessment process that aims to weed out low-quality or *in vitro* only evidence. It also emphasises that a careful and unbiased selection of drug repurposing candidates is required before moving to the clinical setting.