Latest news about drug repurposing in oncology #11

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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

Losartan blocks osteosarcoma-elicited monocyte recruitment, and combined with the kinase inhibitor toceranib, exerts significant clinical benefit in canine metastatic osteosarcoma
Published in Clinical Cancer Research
Spontaneous canine osteosarcoma represents an ideal model for exploring new therapeutic options for both canine and human forms of this disease for which standard of care has not changed in more than three decades. In this trial the combination of losartan, an anti-hypertensive, and toceranib, a TKI, showed clinical benefit (disease stabilisation) in canines with metastatic osteosarcoma through action on the CCR2-CCL2 axis. A Phase I trial in humans (NCT03900793), informed by these results, is now on-going (note that toceranib is approved for

canine cancers, this trial uses losartan with sunitinib which is structurally similar).

Clinical data

Clinical trials

Results of a phase I trial to assess the safety of macitentan in combination with temozolomide for the treatment of recurrent glioblastoma
Published in Neuro-Oncology Advances
Preclinical studies suggest that high dose macitentan, used for pulmonary arterial hypertension, enhances the cytotoxic effects of temozolomide (TMZ) in glioblastoma (GBM), improving survival in animal models. This phase I (n=38) dose-finding trial investigated the combination of macitentan and TMZ in recurrent GBM patients. The trial showed that the combination was safe and tolerable and no maximum tolerated dose was determined. The overall response rate was 13.9% and OS 9.4 months, although the trial was not powered for these end points.

TAXOMET: A French Prospective Multicentric Randomized Phase II Study of Docetaxel Plus Metformin Versus Docetaxel Plus Placebo in Metastatic Castration-Resistant Prostate Cancer
Published in Clinical Genitourinary Cancer
This phase II study (n=99) of docetaxel + metformin vs docetaxel + placebo in metastatic castrate-resistant prostate cancer showed no difference in PFS or OS. The primary end-point was PSA-50 and unexpectedly both treatment and control arms achieved this. This raises further questions about prospects of metformin in this patient population.

Observational studies

Aspirin use and prostate tumor angiogenesis
Published in Cancer Causes & Control
The authors examined associations between regular aspirin use and prostate tumour angiogenesis among 572 men from the Health Professionals Follow-up Study. Prostatectomy tumour blocks were used to assess microvessel size and irregularity. Multivariable linear regression compared use vs nonuse, and by duration and tablets per day. Current aspirin users had larger vessel area (14.5%) and diameter (6.5%), and lower vessel irregularity (− 8.1%) compared to non-users, indicating a less angiogenic profle. Duration of use and current tablets per day were also associated with larger vessel diameter. Similar patterns were seen for low- and high-grade prostate cancers. These findings suggest that

aspirin the protective effects of aspirin in prostate cancer may be due to anti-angiogenic activity.

Preclinical data

Targeting the mitochondrial trifunctional protein restrains tumor growth in oxidative lung carcinomas
Published in The Journal of Clinical Investigation
This pre-clinical study identifies a bio-energetic marker in NSCLC patient samples of paired tumour and adjacent healthy tissue that correlates with outcomes. Furthermore, the group with worse outcomes showed increased expression of HADHA (mitochondrial trifunctional protein). Genetic ablation of HADHA *in vivo* was associated with reduced tumour size. Trimetazidine, an angina drug, was shown to also inhibit HADHA and reduced *in vivo* tumour growth due to inducing redox and energy crisis in tumour cells.

Targeting tumor-stromal IL-6/STAT3 signaling through IL-1 receptor inhibition in pancreatic cancer
Published in Molecular Cancer Therapeutics
The dense stroma associated with pancreatic cancer is associated with resistance to treatment and disease progression. Stromal IL6/STAT3 signalling is a key biomarker of resistance. Building on previous work the authors show that IL1 receptor inhibition reduces IL6 and hence suppresses STAT3 activation. IL1R1 inhibitor anakinra, in combination with gemcitabine, reduces tumour growth and improves survival *in vivo*.

Targeting Pin1 renders pancreatic cancer eradicable by synergizing with immunochemotherapy
Published in Cell
Pin1 is shown to be overexpressed both in pancreatic cells and cancer-associated fibroblasts (CAFs) and correlates with poor patient survival. Targeting Pin1 disrupts the immunosuppressive tumour microenvironment by acting on CAFs. Using the combination of arsenic trioxide and all-trans retinoic acid leads to complete elimination or sustained remissions of aggressive pancreatic cancers by synergising with anti-PD-1 and gemcitabine in diverse model systems.

Functional succinate dehydrogenase deficiency is a common adverse feature of clear cell renal cancer
Published in PNAS
This study demonstrates that underexpression of succinate dehydrogenase (SDH) subunits resulting in accumulation of oncogenic succinate is an epigenetic feature in clear cell renal cell carcinoma (ccRCC). It shows that functional SDH deficiency is a common feature of ccRCC (~80% of all kidney cancers), and not

limited to rare cases with germline SDH mutations. *In vitro* treatment with ascorbic acid reversed the succinate-induced invasiveness of ccRCC cell lines.

Targeting integrated epigenetic and metabolic pathways in lethal childhood PFA ependymomas
Published in Science Translational Medicines
Paediatric posterior fossa group A ependymomas (PFAs) have limited treatment options and often dismal prognoses. This study showed that PFAs overexpress the oncohistone-like protein EZHIP, causing global reduction of repressive H3K27me3, similar to the oncohistone H3K27M. Integrated metabolic analyses in patient-derived cells and tumours and non-invasive metabolic imaging in patients demonstrated enhanced glycolysis and tricarboxylic acid (TCA) cycle metabolism in PFAs. Metformin lowered pathogenic EZHIP protein concentrations, increased H3K27me3, suppressed TCA cycle metabolism, and showed therapeutic efficacy *in vitro* and *in vivo* in patient-derived PFA xenografts in mice.

Niclosamide and Pyrvinium Are Both Potential Therapeutics for Osteosarcoma, Inhibiting Wnt-Axin2-Snail Cascade
Published in Cancers
Oncogenic Wnt signaling pathway and epithelial–mesenchymal transition (EMT) are important in the progression of osteosarcoma. This study investigated whether Axin2, an important EMT target, could be a suitable molecular target and biomarker for osteosarcoma. Patient samples and cell lines showed abundant Axin2. It also showed that the anthelmintic drugs niclosamide and pyrvinium target Axin2, and effectively induce EMT reversion in osteosarcoma cell lines.

Apc-mutant cells act as supercompetitors in intestinal tumour initiation
Published in Nature
Mutations in the APC tumour suppressor gene, which are found in approximately 80% of all human colon cancers, leads to unrestrained activation of the WNT pathway. It has previously been established that Apc-mutant cells have a competitive advantage over wild-type intestinal stem cells (ISCs), thereby out-competing wild-type cells and initiating cancer formation. The mechanisms for this are unclear. This study shows that Apc-mutant ISCs are "supercompetitors" by secreting WNT antagonists and inducing differentiation of neighbouring wild-type ISCs. Lithium chloride, used in bipolar disorder, prevented the expansion of Apc-mutant clones and the formation of adenomas by rendering wild-type ISCs insensitive to WNT antagonists. This suggests that boosting the fitness of healthy cells to limit the expansion of pre-malignant clones may be a powerful strategy to limit the formation of cancers in high-risk individuals.

Other drug repurposing news

Drug repurposing: Misconceptions, challenges, and opportunities for academic researchers

Published in Science Translational Medicine

Begley and colleagues discuss the progress of drug repurposing to date, focusing on oncology and infectious diseases in particular, and the relative lack of regulatory approvals to date. They outline many of the issues around IP, commercialisation, the lack of relevant drug development experience in many repurposing efforts and so on. This is a highly nuanced and relevant discussion for all interested in repurposing.