

## Latest news about drug repurposing in oncology #12

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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](mailto:info@anticancerfund.org)).

### **Top story**

#### [The metabolic adaptation evoked by arginine enhances the effect of radiation in brain metastases](#)

Published in Science Advances

Radiotherapy is a mainstay of treatment for patients with brain metastases irrespective of primary disease - however, radioresistance is common and may be associated with high levels of tumour lactate. Preclinical studies suggest that L-Arginine supplementation may act as a radiosensitiser by reducing the rate of lactate buildup. In a small placebo controlled trial (n=63) oral L-Arginine supplementation was associated with improvements in radiation response and PFS. Along with the correlative biological studies, these results are encouraging and supportive of larger clinical trials.

## Clinical data

### *Clinical trials*

#### [The effect of metformin when combined with neoadjuvant chemotherapy in breast cancer patients](#)

Published in Medical Oncology

In this small trial (n=59) in locally advanced breast cancer, patients were randomised to chemotherapy or chemotherapy + metformin. Results showed no statistically significant difference in pCR between treatment arms.

### *Observational studies*

#### [Impact of Metformin Use on Survival in Patients Undergoing Liver Resection for Colorectal Cancer Metastases](#)

Published in The American Surgeon

Retrospective analysis showing patients with colorectal cancer liver metastases also treated with metformin had better post-surgical resection recurrence-free and overall survival.

### *Case reports*

#### [Mebendazole Mediates Proteasomal Degradation of GLI Transcription Factors in Acute Myeloid Leukemia](#)

Published in International Journal of Molecular Sciences

*In vitro* analysis of the anti-leukemic activity of mebendazole in acute myeloid leukemia (AML) cells via inhibition of the Hedgehog signalling pathway. Two cases of treatment in elderly refractory AML patients are also reported, showing a reduction in blast activity in one of them.

## Preclinical data

#### [Repurposing of posaconazole as a hedgehog/SMO signaling inhibitor for embryonal rhabdomyosarcoma therapy](#)

Published in American Journal of Cancer Research

Embryonal rhabdomyosarcoma is a paediatric soft tissue sarcoma in urgent need of new treatment options. In this *in vitro/in vivo* study the antifungal drug posaconazole was shown to be an active Hedgehog pathway inhibitor that caused growth arrest and induced autophagy in ERMS cells. Oral treatment of mouse with xenograft tumours showed that it slowed tumour growth.

### [Leflunomide Suppresses the Growth of LKB1-Inactivated Tumors in the Immune-Competent Host and Attenuates Distant Cancer Metastasis](#)

Published in Molecular Cancer Therapeutics

Using a wide range of animal models, including patient-derived xenograft (PDX) and immuno-competent genetically engineered lung cancer models, this study shows that the anti-rheumatic leflunomide drug is active against LKB1-mutant cancers. With multiple apparent mechanisms of action, leflunomide was active against both primary tumour growth and also reduced the incidence of lung metastases.

### [IMPDH2 and HPRT expression and a prognostic significance in preoperative and postoperative patients with osteosarcoma](#)

Published in Scientific Reports

Using biopsy and post-surgical tissue from osteosarcoma patients this study analyses the relationship between IMPDH2 and HPRT. The results indicate that low HPRT and high IMPDH2/HPRT ratio are significantly associated with lower overall survival. These results support the use of repurposing candidate mycophenolate mofetil, which targets IMPDH, in osteosarcoma - being investigated in an on-going clinical trial in Thailand (TCTR20190701001)

### [Chlorpromazine induces cytotoxic autophagy in glioblastoma cells via endoplasmic reticulum stress and unfolded protein response](#)

Published in Journal of Experimental & Clinical Cancer Research

This paper presents further exploration of the effects of chlorpromazine in glioblastoma multiforme (GBM). *In vitro* evidence is presented showing that the drug induces autophagy and high-levels of reactive oxygen species in GBM cells, leading to mitotic catastrophe and cell death. A clinical trial by the authors, NCT04224441, is on-going.

## **Other drug repurposing news**

### [Targeting glioblastoma signaling and metabolism with a re-purposed brain-penetrant drug](#)

Published in Cell Reports

Fluoxetine is shown to be a potent anti-glioblastoma drug acting to reduce EGFR signalling and induce lysosomal stress via action on the SMPD1 enzyme. *In vivo* the drug synergises with temozolomide treatment to increase survival in mice bearing orthotopic GBM tumours. Finally, retrospective analysis shows improved survival for GBM patients treated with fluoxetine compared to those treated with other SSRI antidepressants, though the number of patients treated with fluoxetine was very small.

[Retraction for Nojiri et al., Atrial natriuretic peptide prevents cancer metastasis through vascular endothelial cells](#)

Published in PNAS

Article retraction of 'Nojiri et al., Atrial natriuretic peptide prevents cancer metastasis through vascular endothelial cells'

[Drug Repurposing for Rare Diseases: A Role for Academia](#)

Published in Frontiers in Pharmacology

A review of the experience of academic repurposing with orphan medicinal products (OMPs), with focus on three case studies: abatacept for CTLA-4 haploinsufficiency, etidronate for pseudoxanthoma elasticum and mexiletine for non-dystrophic myotonia. The article outlines issues with academic repurposing for OMPS and suggests a number of regulatory changes to overcome these and make repurposing for rare diseases more successful.