IN BRIEF

CANCER

Fighting glioblastoma with vitamin B3

Reactivating the tumour-fighting properties of compromised circulating monocytes and tumour-infiltrating macrophages or microglia could be effective in the treatment of glioblastoma (GBM). Building on previous work, Sarkar et al. now report that niacin (vitamin B3) promotes the stimulation of these myeloid cells in culture. Niacin-exposed monocytes inhibited the growth of brain tumour-initiating cells (BTICs) derived from patients with GBM, through the production of anti-proliferative IFNα14. In mice with intracranial syngeneic or GBM patient-derived BTIC implants, systemic niacin treatment reduced tumour growth and extended survival. These effects were enhanced when niacin was combined with temozolomide.

ORIGINAL ARTICLE Sarkar, S. et al. Control of brain tumor growth by reactivating myeloid cells with niacin. *Sci. Transl Med.* **12**, eaay9924 (2020)

NEUROMUSCULAR DISEASES

Inhibiting hypoxia in muscular dystrophy

There are currently no treatments for facioscapulohumeral muscular dystrophy (FSHD), a genetically complex type of muscular dystrophy caused by abnormal expression of the cytotoxic double homeobox protein 4 gene (*DUX4*). Using a genome-wide CRISPR–Cas9 loss-of-function screen in a muscle cell line, Lek et al. discovered that the cellular hypoxia response pathway plays a key pathogenic role in mediating DUX4-induced cell death. Hypoxia signalling inhibitors circumvented cell death in DUX4-expressing cells, reduced FSHD disease biomarkers in patient myogenic lines and induced structural and functional improvements in zebrafish models of FSHD.

ORIGINAL ARTICLE Lek, A. et al. Applying genome-wide CRISPR-Cas9 screens for therapeutic discovery in facioscapulohumeral muscular dystrophy. *Sci. Transl Med.* **12**, eaay0271 (2020)

ANTICANCER AGENTS

Combination therapy combats aggressive breast cancer

Triple-negative breast cancer (TNBC) is an aggressive form of breast cancer with limited therapeutic options. Schafer et al. report that a substantial fraction of primary TNBCs express MYCN and that the fraction of tumour cells expressing MYCN is even higher in residual TNBC after chemotherapy. A high-throughput screen on TNBC cell lines revealed that higher expression of MYCN was associated with greater sensitivity to BET inhibitors. The combination of BET and MEK inhibitors synergistically decreased tumour cell viability in MYCN-expressing TNBC cells and patient-derived xenograft models.

ORIGINAL ARTICLE Schafer, J. et al. Targeting MYCN-expressing triple-negative breast cancer with BET and MEK inhibitors. *Sci. Transl Med.* **12**, eaaw8275 (2020)

PSYCHIATRIC DISORDERS

Fast-fail approach identifies promising anhedonia therapy

The NIMH fast-fail treatment development approach incorporates biomarker-based proof-of-mechanism testing in phase II, to determine whether engaging the target of interest has the intended neurobiological effects. Krystal et al. now report findings of the first comprehensive application of this approach, evaluating the potential of the κ-opioid receptor antagonist JNJ-67953964 in the treatment of patients with anhedonia and a mood or anxiety disorder. JNJ-67953964 significantly increased ventral striatum activation during reward anticipation compared with placebo, improved clinical measures of anhedonia and was generally well tolerated without signs of serious adverse events.

ORIGINAL ARTICLE Krysta, A. et al. A randomized proof-of-mechanism trial applying the 'fast-fail' approach to evaluating κ-opioid antagonism as a treatment for anhedonia. *Nat. Med.* https://doi.org/10.1038/s41591-020-0806-7 (2020)

Credit: dcdebs/E+

CANCER

TGFβ1-specific antibody spurs anti-tumour immunity

Transforming growth factor-β (TGFβ) signalling is associated with tumorigenesis and resistance to checkpoint inhibitors (CPIs). Schürpf and colleagues now show that the TGFβ1 isoform is frequently overexpressed in multiple cancer types and that a TGFβ1-specific antibody renders CPI-resistant tumours sensitive to immunotherapy.

In The Cancer Genome Atlas (TCGA), the authors found that TGFβ1 is the most prevalent TGFβ isoform in multiple human cancers, including many that are treated with CPIs. Furthermore, TGFβ1 mRNA levels correlated with a transcriptional signature of innate anti-PD1 resistance.

Previous work suggested that TGFβ mediates resistance to CPIs, but many anti-TGFβ therapies are cardiotoxic and therefore have limited therapeutic potential. TGFβ contains a prodomain that has comparatively little sequence identity between the three TGFβ isoforms, and the pro-protein assembles extracellularly into large latent complexes (LLCs) with TGFβ-binding proteins. The authors reasoned that anti-LLC antibodies, which could bind to the prodomain, may be isoform-specific. They purified TGFβ1-containing LLCs, screened a naive human antibody library and identified SRK-181 as a TGFβ1–LLC-selective antibody.

SRK-181 bound to TGFβ1-containing LLCs through three regions, including the prodomain of TGFβ1, but not to active TGFβ or LLCs containing other TGFβ isoforms. SRK-181 prevented TGFβ1 activation in cell-based assays.

Three mouse syngeneic tumour models — one bladder cancer, one breast cancer and one melanoma — that had primary resistance to CPIs, lacked T cell infiltration, expressed TGFβ1 and had activated TGFβ signalling were chosen to evaluate the antibody. In all three models, the combination of a murine version of SRK-181 and anti-PD1 treatment reduced tumour burden. In most complete responders, the tumours did not regrow after treatment discontinuation, suggesting durable immunological antitumour memory.

Tumours treated with the combination therapy had ten times more $CD8^+$ T cells than those treated with control antibodies. Markers for inflammation-inhibiting M2-like macrophages and myeloid-derived suppressor cells, two known immune inhibitory cell types in the tumour microenvironment, were also decreased in tumours from mice treated with the combination therapy.

The cardiotoxicity of pan-TGFβ inhibitors and molecules that target the TGFβ receptor is likely because they inhibit TGFβ2 and/or TGFβ3 signalling in cardiac tissue. Treatment with SRK-181 at the highest dose tested, however, did not cause valvulopathies or other histological signs of cardiotoxic effects.

These results suggest that selective TGFβ1 inhibition could be a useful therapeutic strategy to sensitize certain tumours to CPIs. They also highlight the potential for targeting protein complexes and prodomains to achieve isoform selectivity.

Megan Cully

ORIGINAL ARTICLE Martin, C. J. et al. Selective inhibition of TGFβ1 activation overcomes primary resistance to checkpoint blockade therapy by altering tumor immune landscape. *Sci. Transl Med.* **12**, eaay8456 (2020)
RELATED ARTICLE Galon, J. & Bruni, D. Approaches to treat immune hot, altered and cold tumours with combination immunotherapies. *Nat. Rev. Drug Discov.* **18**, 197–218 (2019)