...the advent of CAR T cell therapy shows the potential of targeting treatment to cell-surface markers...

NEPC, and adenocarcinoma-specific expression of STEAP1, FXYD3, and FOLH1 (PSMA) and NEPC-specific expression of NCAM1, SNAP25, and CEACAM5 were validated using immunoblot and immunohistochemistry (IHC) of cell lines and xenografts. Tissue microarray and IHC of benign and malignant prostate tissue validated FXYD3 as a tumour antigen in adenocarcinoma, whereas CEACAM5 was identified for NEPC.

Given that CEACAM5 is under investigation as a therapeutic target in colorectal cancer, the team went on to study whether it had the same potential in NEPC. They generated CEACAM5 CAR T cells and co-cultured these with NEPC cells, showing >80–90% cell kill within 48h, supporting CEACAM5 as a promising target antigen for NEPC.

Annette Fenner

ORIGINAL ARTICLE Lee, J. K. et al. Systemic surfaceome profiling identifies target antigens for immune-based therapy in subtypes of advanced prostate cancer. *Proc. Natl Acad. Sci.* <https://doi.org/10.1073/pnas.1802354115> (2018)

FURTHER READING Davies, A. H. et al. Cellular plasticity and the neuroendocrine phenotype in prostate cancer. *Nat. Rev. Urol.* **15**, 271–286 (2018)

treatment with MMAF–E3 ... significantly inhibited tumour growth and prolonged survival

targeting at a 1:1 ratio of antidote:E3. In a subcutaneous prostate tumour model in mice, treatment with MMAF–E3 but not with the nontargeted control significantly inhibited tumour growth and prolonged survival compared with a saline control.

“We demonstrate for the first time that highly toxic aptamer–drug conjugates can inhibit tumour growth and improve survival in mice, creating a new class of anticancer agent,” summarizes Powell Gray. Senior author Bruce A. Sullenger describes the implications of the work: “Because aptamers are synthetic and not biological agents, we believe that this approach will ultimately yield inexpensive, yet highly targeted anticancer agents, which is expected to result in a major economic benefit to the health-care system (as current antibody-based drugs are expensive) and to improve patient accessibility to therapy.”

Clemens Thoma

ORIGINAL ARTICLE Powell Gray, B. et al. Tunable cytotoxic aptamer–drug conjugates for the treatment of prostate cancer. *Proc. Natl Acad. Sci. USA* **115**, 4761–4766 (2018)

BLADDER CANCER

In the bank: bladder organoids recapitulate original tumour

A biobank of patient-derived bladder cancer organoids that faithfully recapitulate the original tumour has been developed. Drug responses observed in organoids also occur in vivo, so these organoids could eventually be used to guide treatment decisions.

The biobank of organoids was established from fresh transurethral resection samples and the diversity of the organoids in the biobank is representative of the patient population from which it was generated. Overall, 16 organoid lines were established from 16 patients, multiple organoid lines were generated from 3 patients, representing chronologically distinct

lesions. Established lines underwent multiple passages, cryopreservation, and recovery. Morphological concordance between the organoids and their parental tumours was strong. Histological analysis of organoid-derived xenografts and organoids derived from these xenografts showed that they were similar to the parental tumour.

The mutational profile of organoids and their parental tumours was highly concordant, and organoid mutations recapitulated the majority of common genomic alterations observed in human bladder cancer. Mutation profiles within individual organoid lines and their derivatives were also similar. Subclonal mutations were gained or lost during serial passaging, grafting, and/or re-establishment of organoids. Phylogenetic analysis showed linear and branched tumour evolution patterns, but the extent of evolution varied between organoid lines.

Organoid lines could be separated into two general categories: one group had strong phenotypic stability with similar marker expression profiles between the parental tumour, passaged organoids, xenografts, and xenograft-derived organoids; and the second group displayed considerable phenotypic differences between the parental tumours and organoids. In this second group, in most cases the parental tumour predominantly or exclusively expressed luminal markers, whereas the organoids lost luminal-marker expression and gained basal markers, but reverted back to a luminal phenotype when they were grown as xenografts. Organoids could be successfully categorized into basal or luminal subtypes using a molecular classifier based on human studies of bladder cancer, but several displayed a mixed phenotype.

Organoid response to bladder cancer drugs correlated with tumour progression. The mutational profiles of organoids could be used to predict additive drug responses. Validation of drug responses using xenograft studies showed that drug responses in culture were recapitulated in vivo. Overall, this new biobank of bladder cancer organoids faithfully recapitulates the histology and molecular landscape of the original tumours and can be serially passaged, cryopreserved, and xenografted. In the future, these organoids could be used to aid treatment decisions for patients with bladder cancer.

Louise Stone

ORIGINAL ARTICLE Lee, S. H. et al. Tumor evolution and drug response in patient-derived organoid models of bladder cancer. *Cell* **173**, 515–528 (2018)

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