531 UNRAVELLING MECHANISMS OF RESISTANCE TO IMMUNE CHECKPOINT BLOCKADE USING A LINEAGE-TRACING TOOL, CATCH

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Background The immune system is a formidable force capable of recognizing and eliminating aberrant cells arising due to malignant transformation. Immunotherapies (IT) aim to capitalize on this naturally occurring defence system and have revolutionized cancer treatment over the past decade. The greatest obstacle to the resounding success of IT however, is resistance. A large proportion of patients never respond (inherent resistance), and of those that do, many relapse (acquired resistance).[1] How immunotherapy-resistant cells emerge, and which mechanisms of resistance are frequently employed by cancer cells remains an important but so far poorly understood clinical problem. Answers to these questions will provide insights into fundamental processes of immunology and provide the basis for designing rational therapeutic regimens.

Methods Employing a novel functional lineage tracing tool developed in our lab (CaTCH),[2] we have traced individual cells following *in vivo* immunotherapy treatment and isolated living populations for downstream functional analysis.

Results Using this system, we have isolated a clonal pair from both a heterogeneous treatment-naïve population (treatment-naïve; TN), as well as from a population exposed to IT *in vivo* that initially responded to therapy but subsequently relapsed (resistant; R). We have functionally tested these clones both *in vitro* and *in vivo*, determining an acquired and cell-intrinsic mode of resistance in the treatment-exposed clone.

Conclusions Our work further aims to mechanistically define how this resistance is achieved, equipping us with the knowledge to intervene and potentially reverse or prevent its emergence.

REFERENCES

1. Sharma, P., Hu-Lieskovan, S., Wargo, J. A. & Ribas, A. Primary, Adaptive, and Acquired Resistance to Cancer Immunotherapy. *Cell* 2017;**168**, 707–723.
2. Umkehrer, C. *et al.* Isolating live cell clones from barcoded populations using CRISPRa-inducible reporters. *Nat. Biotechnol. 2020 392* **39**, 174–178 (2020).

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