Uncoupling Efficacy from Toxicity: A Case Study on MEDI5752

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As discussed in our related commentary[a], the excitement ignited by immune checkpoint inhibitor therapies is curbed by the serious adverse effects that these treatments can cause. Much effort is now focused on developing new drugs that can target cancer cells as efficiently as existing treatments, but without the collateral damages on healthy tissues, i.e., uncoupling efficacy from toxicity.

CTLA-4 blockade has been linked to the appearance of grade 3–4 immune-related adverse effects (irAEs), including hematological, hepatic, endocrine, gastrointestinal, neurologic, and dermatological damages.[1,2] This major limitation has revealed the necessity to develop new antibodies directed against CTLA-4 that exhibit reduced toxicity. AstraZeneca recently developed MEDI5752, a monovalent bispecific antibody (BsAb) that simultaneously binds hPD-1 and hCTLA-4.

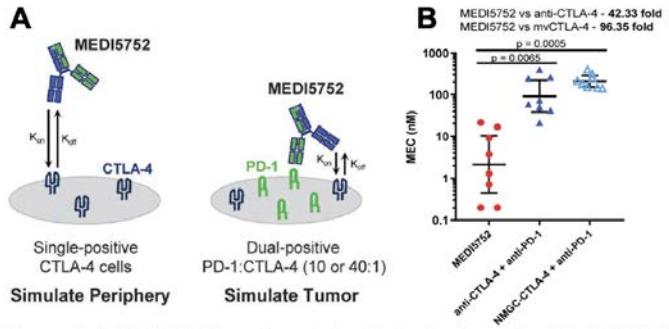

Figure 1 / MEDI5752 preferentially binds dual-positive PD-1⁺/CTLA-4⁺ cells at the tumor as represented in (A) and shows reduced Minimum Effective Concentration (MEC) in a PBMC assay, compared to conventional antibodies (B). Adapted from Dovedi et al., Cancer Discovery, 2021.

In a paper recently published in *Cancer Discovery*, Dovedi et al. showed that this BsAb preferentially and efficiently binds PD-1⁺/CTLA-4⁺ double-positive cells rather than PD-1⁻/CTLA-4⁺ single-positive cells by co-operative binding. This favors the compound's distribution to the tumor, rather than to other healthy tissues (Fig.1A), and suggests that MEDI5752 can preferentially inhibit CTLA-4 on PD-1⁺ activated vs. non-activated T cells. Interestingly, the authors showed that their BsAb can be efficient *in vitro* at significantly lower concentrations than conventional antibodies used in combination therapies (Fig.1B).

To assess their compound's distribution and efficacy *in vivo*, hPD-1/hCTLA-4 mice[b] were subcutaneously implanted with MCA205 tumors, and subsequently injected with radiolabeled MEDI5752, anti-PD-1, anti-CTLA-4 or isotype hIgG monoclonal antibodies (mAbs). By monitoring antibody biodistribution and tumor volume, the authors showed that MEDI5752 preferentially localizes and accumulates in tumors (Fig.2A).

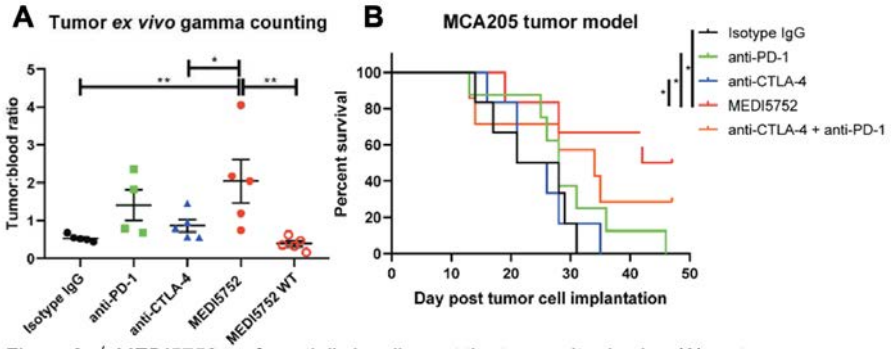

Figure 2 / MEDI5752 preferentially localizes at the tumor sites in vivo *(A) and increases survival (B) of double humanized PD-1/CTLA-4 mice subcutaneously implanted with MCA205 tumors. Adapted from Dovedi et al., Cancer Discovery, 2021.*

MEDI5752 also displayed a strong and dose-dependent anti-tumor activity, demonstrating the bispecific antibody's efficacy. Additionally, a single dose of MEDI5752 led to increased survival compared to anti-PD-1 and/or anti-CTLA-4 mAbs treatments (Fig.2B).

These data demonstrate the efficacy of this new bispecific antibody MEDI5752 over conventional combination therapy, and suggest that its preferential localization to the tumor could reduce treatment-associated adverse effects.

Interestingly, two patients with advanced solid tumors positively responded to MEDI5752 treatment, thus supporting the translational relevance of these findings. Taken together, these findings show that MEDI5752 represents a novel immunotherapy that provides modulated CTLA-4 inhibition while suppressing the PD-1 pathway, thereby uncoupling CTLA-4-dependent peripheral toxicity from anti-tumor efficacy.[3]

Of note, the double humanized mouse preclinical model used in this study was generated by genOway, designer and provider of multiple preclinical models[(c)] in immuno-oncology. This specific model enables the *in vivo* efficacy assessment and profiling of immuno-oncology agents targeting the human immune checkpoint PD-1 and/or CTLA-4 in fully immunocompetent mice. Importantly, it has been co-validated by partners of the precompetitive consortium[(d)] of company leaders in immuno-oncology and immunotherapy.

See also:
Uncoupling Toxicity from Therapeutic Efficacy: A Case Study on ATOR-1015
https://www.genoway.com/case-studies/ator-1016.htm

References:

1. Omar NE, El-Fass KA, Abushouk AI, et al. Diagnosis and Management of Hematological Adverse Events Induced by Immune Checkpoint Inhibitors: A Systematic Review. *Front Immunol.* 2020;11:1354. doi:10.3389/fimmu.2020.01354
2. Du X, Liu M, Su J, et al. Uncoupling therapeutic from immunotherapy-related adverse effects for safer and effective anti-CTLA-4 antibodies in CTLA4 humanized mice. *Cell Res.* 2018;28(4):433-447. doi:10.1038/s41422-018-0012-z
3. Dovedi SJ, Elder MJ, Yang C, et al. Design and efficacy of a monovalent bispecific PD-1/CTLA-4 antibody that enhances CTLA-4 blockade on PD-1+ activated T cells. *Cancer Discov.* Published online January 8, 2021. doi:10.1158/2159-8290.CD-20-1445

(a) https://www.genoway.com/commentaries/uncoupling-toxicity-from-therapeutic-efficacy.htm
(b) https://www.genoway.com/catalog/humanized-immune-checkpoints/dt/pd-1-ctla-4.htm
(c) https://www.genoway.com/catalog/overview.htm
(d) https://www.genoway.com/about/genoway/news/2019/icp-consortium.htm