Immune biology modulation with synthetic TCR and NK receptors – strengthening the foothold in solid tumors

In the much-publicized immunotherapy arena, new technologies and mechanisms are being utilized to harness the immune system to eradicate cancer. Despite risky unknowns, synthetic immunity is becoming a reality in solid tumors with new technologies, approaches, and cell types. These cell types use T-cell platforms (TILs, CARs, and TCRs) or innate immune cell platforms (NK cells, dendritic cells, cytokine induced killer cells, TILs, and mesenchymal stromal cells).

A few approaches have continued to be the focus of innovation. These approaches include enhancing T-cell functions, overcoming T-cell suppression/exhaustion in the tumor microenvironment (TME), improved safety, mitigating risk of rejection (reduce alloreactivity), novel NK cell design, engineered TCR cell therapies, and improvement in manufacturing process.

ESMO 2021 reflected the trends. While sustained clinical efficacy was noted in some ongoing studies with CAR-T and TCR T-cell therapies, promising preclinical outcomes were also observed with novel, synthetic NK cell receptor constructs to engage innate immunity.

New constructs improve the speed of T-cell receptor fusion constructs (TRUCs) and spearhead the development of 'spear cells'; cancer testis antigens, mesothelin, and HER2 are still promising targets.

TCR² Therapeutics reported exceptional interim results with its gavo-cel (TC-210), a mesothelin targeted TRUC in all three mesothelin-expressing tumors (ovarian, mesothelioma and cholangiocarcinoma) in a dose escalation study. TRUC-T is comprised of an anti-MSLN single domain antibody fused to the CD3ε subunit thus eliminating the need for HLA matching.

- Interim efficacy read-outs showed that 15/16 patients responded to the treatment with ≥50% regression in tumor lesions in 6/16 patients. Interestingly, most of the mesothelioma patients showed this regression at dose level 1. Most patients in the study were heavily pretreated with median of 5 lines of prior therapies including checkpoint and mesothelin-targeted therapies. The study also reported mPFS and mOS benefit in refractory mesothelioma patients indicating promise of the therapy in the tumors with a high unmet need.[1]

Harnessing the CD4+ cell functions, Adapt-immune Therapeutics continued to describe promising data with ADP-A2M4CD8 SPEAR T-cells in multiple tumor types from the ongoing Phase I SURPASS trial (NCT04044859). ADP-A2M4CD8, next-generation CD4+ SPEAR T-cells, co-express CD8α co-receptor and engineered MAGE-A4c1032 TCR to increase TCR-binding avidity and enhance the polyfunctional response of engineered CD4+ T-cells against MAGE-A4+ tumors. The modifications introduced in the construct enable CD4+ T-cells to kill tumor cells and improve cross-talk with APCs while retaining helper functions.

- Durable clinical response of SPEAR T-cells was observed in multiple solid tumors with 36% ORR (N=22 evaluable patients) -- **a CR and PR in ovarian cancer and PRs in HNSCC, synovial sarcoma, and GEJ cancer.**[2] The SPEAR T-cells were persistent (present in the peripheral blood up to 320 days post-infusion) and expanded post-infusion. **A Phase II SURPASS-2 trial is planned for esophageal and GEJ cancers.**

While TCR therapies have strong potential, their efficacy is limited by inhibitory TME. **Introduction of chimeric co-stimulatory receptor in transgenic T-cells effectively confronted the hostile TME.** Medigene highlighted that inhibitory signals mediated by tumor PD-L1 can be turned into stimulatory signal by co-expression of PD-1/4-1BB receptor with their TCR lead candidate (TCR-4). TCR-4 is directed against HLA-restricted PRAME epitope.[3]

- Co-expression resulted in enhanced cytokine release, TCR T-cell proliferation upon antigenic stimulation, improved killing of PD-L1-positive tumor cells, and complete eradication of the tumor in mice melanoma model.[3]

TCR T-cell therapies hold promise to treat poor prognosis patients refractory to multiple lines of treatment. Key questions to address:

- What is the competitive differentiation vs. other modalities (T-cell engagers, ADCs, and CAR-Ts) against the same target? In the same tumor?
- What is the optimal positioning of these therapies (patient segment/line of therapy)?
- What is the body of evidence in diverse populations with novel TCR constructs designed to impart HLA independent functions?

Antibody-based NK cell Engager Therapeutics (ANKETs) and tri-specific killer engager (TRIKEs) represent potential innovations in NK cell engagement to improve risk-benefit profile. Can they replace BiTEs and conventional antibodies?

There is a growing interest in harnessing innate immunity against cancer. NK cell science is emerging as the next wave immunotherapy. **Innate Pharma showcased its versatile, fit-for-purpose, multi-specific NK cell engagers platform ANKET.**[4] Tetraspecific ANKETs not only co-engage NKp46 and CD16 on NK cell and tumor antigen on tumor cells for efficient tumor killing but also express IL2v that provides specific NK cell proliferation and activation signals. NKp46 expression is conserved on tumor-infiltrating NK cells. No statistically significant downregulation of NKp46 is observed in several cancer conditions which makes them a very specific marker of human NK cells.

- Tetraspecific ANKETs were more potent and demonstrated single agent activity in aggressive hCD20-B16F10 tumor model. In non-human primates, ANKET showed sustained CD20+ B-cell depletion, longer PK with minimal systemic cytokine release, and no clinical sign of toxicity.

GT Biopharma also advanced its second-generation TriKE (GTB-3650) into IND-enabling studies for the treatment of relapsed/refractory AML and high-risk MDS[5]. The construct is based on camelid single-domain antibody (VHH) instead of scFv that confers many advantages over conventional IgG-based antibodies. These advantages include high affinity and specificity, high thermostability, good solubility, relatively low production cost, flexibility for modular format, low immunogenicity, and higher penetration rate into tissues.

- Preclinical data of camTriKEs against HER2 and B7 H3 tumors was presented. Cam16/IL15/ScFv HER2 TriKE expressing IL15 and directed against HER2 antigen was highly effective in ovarian cancer model. IL15 moiety triggered NK cell expansion and priming. GTB-3650 has shown significantly higher potency than first generation ScFv-based GTB-3550 in preclinical models.

Advancing NK cell therapies a step further, **Acepodia** also reported pre-clinical and early clinical activity of their **first-in-class, off-the-shelf, selected NK cell product ACE1702 in HER2+ tumors[6].** These are trastuzumab-armed selected NK cell based on antibody-cell conjugation (ACC) platform.

- Escalation study of ACE 1702 in subjects with HER2-expressing solid tumors (NCT04319757) showed that while ACE 1702 was well tolerated, efficacy was moderate with one PR in a salivary gland tumor patient.

As ANKETs and TRIKEs platforms advance NK cell therapies a step further, key questions are:

- What is the value proposition of NK cell based therapies vs. T-cell therapies and T-cell engagers? Are there any indicators of monotherapy potential?
- Which construct designs are likely to be more successful?
- Which tumors are likely to have higher role for NK cell therapies based on biology and tumor microenvironment?
- Which partners will drive a successful combination strategy?

Cytokines find continued use as adjuncts to cell therapies; appropriate cytokine and cell therapy match will become important as novel cytokines join the armamentarium.

Engineered cytokines such as IL-2, IL-15, and IL-12 have shown potential as standalone therapy as well as adjunct in cell therapies. In a session on '**overview of synthetic immune receptors**' Dr. Hinrich Abken (Professor and Chair for Genetic Immunotherapy, Regensburg University; Director, the Center for Interventional Immunology) showed that use of IL-18 in **TRUCKs was superior over IL-12** in controlling large tumors in syngeneic mice models. IL18 was more effective in improving the cytolytic T-cell performance by inducing T-Bet high and FOXO1 low effector T-cells compared to other cytokines. These early findings will have implications on choice of cytokine to be incorporated in future cell therapies.

The emerging field of synthetic immunology is assembling a large arsenal of tools that can be used to enhance or reprogram the immune system against cancer. Next-generation T-cells and NK cells with synthetic immune receptors are more **potent**. These cells have **high bio-distribution and** are showing promising efficacy/safety in the preclinical and clinical setting to overcome some of the limitations of CAR-T therapy and other antibody approaches.

References

1. D. S. Hong, S. L. SciMentum, J. Tanyi, et al. Gavocabtagene autoleucel (gavo-cel, TC-210) dose escalation in refractory mesothelin-expressing solid tumors. [Abs# 959O]. In: ESMO 2021; Sept 16-21. Available at: https://oncologypro.esmo.org/meeting-resources/esmo-congress-2021/gavocabtagene-autoleucel-gavo-cel-tc-210-dose-escalation-in-refractory-mesothelin-expressing-solid-tumors.
2. D. S. Hong, J. M. Clarke, A. Asch, et al. Safety and efficacy from the SURPASS trial with ADP-A2M4CD8, a SPEAR T-cell therapy incorporating a CD8α co-receptor and an affinity optimized TCR targeting MAGE-A4. [Abs# 540P]. In: ESMO 2021; Sept 16-21; Paris, France. Available at: https://oncologypro.esmo.org/meeting-resources/esmo-congress-2021/safety-and-efficacy-from-the-surpass-trial-with-adp-a2m4cd8-a-spear-t-cell-therapy-incorporating-a-cd8a-co-receptor-and-an-affinity-optimized-tcr.
3. M. Bürdek, I. Fetzer, N. Sailer, et al. T-cells transgenic for a highly potent PRAME-specific TCR and a chimeric PD1-41BB co-stimulatory receptor represent a promising approach for the treatment of solid tumors. [Abs# 1007P]. In: ESMO 2021; Sept 16-21; Paris, France. Available at: https://oncologypro.esmo.org/meeting-resources/esmo-congress-2021/t-cells-transgenic-for-a-highly-potent-prame-specific-tcr-and-a-chimeric-pd1-41bb-co-stimulatory-receptor-represent-a-promising-approach-for-the-tr.
4. E. Vivier, M. Vetizou, A. B. Alvarez, et al. Harnessing innate immunity in cancer therapies: The example of natural killer cell engagers. [Abs# 1O]. In: ESMO 2021; Sept 16-21; Paris, France. Available at: https://oncologypro.esmo.org/meeting-resources/esmo-congress-2021/harnessing-innate-immunity-in-cancer-therapies-the-example-of-natural-killer-cell-engagers.
5. J. S. Miller, E. D. Warlick, R. Wangen, et al. GTB-3550 tri-specific killer engager safely activates and delivers IL-15 to NK cells, but not T-cells, in immune suppressed patients with advanced myeloid malignancies, a novel paradigm exportable to solid tumors expressing Her2 or B7H3. [Abs# 965MO]. In: ESMO 2021; Sept 16-21; Paris, France. Available at: https://oncologypro.esmo.org/meeting-resources/esmo-congress-2021/gtb-3550-tri-specific-killer-engager-safely-activates-and-delivers-il-15-to-nk-cells-but-not-t-cells-in-immune-suppressed-patients-with-advanced.
6. S. A. Piha-Paul, D. Mahalingam, M.F. Mulcahy, et al. ACE1702, a first-in-class, off-the-shelf, selected natural killer cell [oNK] product using antibody cell conjugation technology [ACC], with pre-clinical and early clinical activity in HER2 < 3+ tumors. [Abs# 1006P]. In: ESMO 2021; Sept 16-21; Paris, France. Available at: https://oncologypro.esmo.org/meeting-resources/esmo-congress-2021/ace1702-a-first-in-class-off-the-shelf-selected-natural-killer-cell-onk-product-using-antibody-cell-conjugation-technology-acc-with-pre-cli.

SmartAnalyst is helping clients interpret the data presented at ESMO 2021 focusing on key developments in cancer research. ***Contact us to learn more***

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