LifeSci Capital KOL Series – T-Cell Receptor Technology and CAR-T

We hosted a Key Opinion Leader dinner with Dr. Michel Sadelain and Dr. Michelle Krogsgaard to discuss adoptive T-cell therapies including T-cell receptor (TCR) and chimeric antigen receptor (CAR) technologies. Dr. Sadelain is the Director of the Center for Cell Engineering at Memorial Sloan-Kettering Cancer Center and coined the term CAR in CAR-T. Dr. Krogsgaard directs the Krogsgaard laboratory at NYU Langone Medical center. They are leading academics focused on adoptive T-cell therapies, and provided an overview of the science behind this exciting new field. Below we discuss T-cell receptor technology, cancer antigen selection, differences between TCR and CAR-T, and the future of CARs in solid tumors.

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- **T-Cells Must be Engineered to Recognize and Bind to Certain Cancer Antigens**. One of the great deceptions of tumor cells is their ability to evade detection by the body's immune system since they mostly express and present normal proteins. Correspondingly, a primary challenge for cancer treatment is to train the immune system to recognize these cancer cells as foreign and attack them. T-cells that bind strongly to self-antigens are deleted in the thymus, and so a patient is unlikely to have T-cells that bind to tumor-derived antigens with only minor differences from normal proteins. Furthermore, the evolution of tumors leads to the selection of tumor cells with decreased antigen and major histocompatibility complex (MHC) expression. For these reasons, self-derived antigens overexpressed in various tumors do not elicit an adequate immune against the cancer. The KOLs noted that to overcome these issues, T-cell receptors can be engineered *ex vivo* to bind target antigens with enough affinity to trigger immune-mediated anti-tumor attack.

- **Antigen Discovery will be a Rate Limiting Step in TCR Development**. Antigens targeted by immunotherapy must be differentially expressed on tumors and elicit a response by the host immune system, which makes them difficult to identify. Dr. Sadelain and Dr. Krogsgaard discussed two overarching antigen discovery strategies:
  - One strategy is to sequence each patient's tumor to identify neo-antigens, which are novel protein sequences not previously detected by the immune system that are often restricted to a single patient. This approach is highly personalized and current technologies are not capable of generating TCR candidates for individual patients.
  - The second strategy, preferred by Dr. Sadelain, is to target shared antigens presented by a large population of people. Examples include the cancer testis antigens NY-ESO-1 and MAGE, which are overexpressed by a wide range of cancers including myeloma, ovarian cancer, non-small-cell lung cancer, and melanoma. These antigens are not expressed after fetal development in normal cells, making them an attractive shared antigen target for T-cell therapy.

Dr. Sadelain also indicated that viral antigens are easily recognized by TCRs and are good antigens. However, these antigens are likely the low hanging fruit, and it will be challenging to identify additional antigens with broad cancer expression, that are high immunogenic, and that are not expressed on normal tissues.

- **TCR Candidates Must be Screened for Off-Target Toxicities.** Part of the challenge in identifying new antigens is the process of screening TCR candidates for off-target toxicities. Dr. Sadelain discussed a particular case where off-target reactivity was observed with a high-affinity TCR engineered to target a peptide derived from MAGE A3. This engineered TCR unexpectedly reacted against a structurally similar but functionally unrelated peptide from the muscle protein Titin, leading to fatal cardiac toxicity in two patients. The expression of Titin in cardiac tissue was not observed in initial two-dimensional culture models, but was later observed in a three-dimensional culture system. Dr. Krogsgaard indicated that a humanized mouse model can also be used to screen for potential off-target reactivity against HLA-peptides. The case of cardiac toxicity highlights the need for extensive screening for off-target binding prior to clinical trial initiation. Leading companies in the space have developed protocols to minimize these safety risks. In particular, Immunocore (private) has developed an *in vitro* molecular analyses to assess TCR specificity against a panel of peptide variants. Adaptimmune (NasdaqGS: ADAP) has also added an extra layer of screening in preclinical models to determine if other proteins in normal tissues mimic target antigens.

- **HLA Matching is a Challenge for TCR Engineering.** Intracellular antigens are presented to immune cells via a display mechanism called the human leukocyte antigen (HLA) system. T-cell receptors bind to peptide-HLA complexes on the cell surface and must

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recognize both the antigen and the HLA. The challenge for TCR engineering is that several HLA genotypes exist, and a single engineered TCR will not work in all patients who share an antigen. For example, the HLA-A*0201 restricted peptide, one of the most common HLA subtypes, would only be applicable to roughly 50% of Caucasian patients in the US. In Adaptimmune's NY-ESO-1 trial, only 24/70 screened patients were eligible for enrollment based on their HLA subtype. Due to these constraints, Dr. Sadelain highlighted the need to target up to 7 different HLAs to cover the majority of patients. This puts a strain on the discovery and engineering process post-antigen selection.

- **TCRs and CARs have Distinct Properties that are Advantageous for Certain Tumor Profiles**. Chimeric antigen receptor technology (CAR-T) is a type of adoptive T-cell approach that fuses antibody recognition domains to T-cells. The approach is applicable to cancers with cell surface antigens, and initial clinical data in relapsed/refractory B-cell acute lymphocytic leukemia (ALL) have been impressive with complete response rates reaching 90%. Several companies such as Novartis (NYSE: NVS), Juno (NasdaqGS: JUNO), Kite (NasdaqGS: KITE), and Bellicum (NasdaqGM: BLCM) are pushing forward with clinical programs targeting the CD19 antigen and others. TCRs can potentially target a much larger pool of antigens compared to the CAR-T approach, given that the majority of tumor antigens are presented by HLA complexes, whereas CAR-T only targets cell surface antigens. Overexpressed antigens, sometimes expressed 100 to 1,000 times greater on the tumor surface, are much better targets for CARs compared to TCR. However, developmental antigens such as NY-ESO-1 and MAGE are mostly present in the cytoplasm, making them inaccessible to CARs.

  Dr. Sadelain indicated that TCRs are natural biological systems that are inherently designed to recognize foreign antigens. Antibody-derived CARs on the other hand are engineered to recognize a particular cancer antigen. The limiting step in engineering an efficient CAR is selecting an appropriate tumor antigen. In addition to targeting selected tumor antigens, TCRs need to be engineered to have an increased affinity to the selected target. Noting the success seen in 2nd generation CARs, Dr. Sadelain and Dr. Krogsgaard expressed optimism in the potential to introduce co-stimulation in engineered TCRs to heighten *in vivo* performance. Engineering TCRs with chimeric elements, similar to CARs, can potentially boost T-cell persistence and proliferation *in-vivo*. It was also mentioned that TCRs have a toxicity profile that is far more unpredictable than CARs.

- **Soluble TCRs are an Attractive Strategy at its Infancy**. Soluble TCRs are not directly attached to a T-cell and instead link cancer cells with the immune system. For example, Immunocore (private) has developed bi-specific molecules comprising an engineered TCR-based targeting system fused to an anti-CD3 effector function. The TCR binds to cancer cells displaying tumor antigens, and the anti-CD3 component binds and activates T-cells. Both Dr. Krogsgaard and Dr. Sadelain agreed that engineering soluble TCRs is an attractive strategy that needs to be validated with more clinical data. Soluble receptors have the potential to easily degrade in the body, leading to less toxicity. However, soluble molecules with a limited half-life may reduce potency, leading to fewer responses with and less durability.

- **CD19 CARs Continue to Show Improvement in ALL.** Dr. Sadelain gave an update on Memorial Sloan Kettering Cancer Center's (MSKCC) CD19 CAR program in ALL.
  - Second generation CARs, incorporating the CD28 co-stimulatory domain, have allowed T-cells to persist longer. Dr. Sadelain noted that in fact, 3 patients in the MSKCC's trial are still expressing anti CD-19 T-cells after 2+ years.
  - Currently, patients with relapsed/refractory ALL who achieve a complete response with CAR treatment may proceed on to an allogeneic hematopoietic stem cell transplant (HSCT). Dr. Sadelain believes that CAR therapy can be used as a stand-alone therapy. He noted that CARs are demonstrating the potential to induce durable complete responses in patients.
  - Approximately 6% of CD19-negative patients relapsed from CAR therapy in a trial conducted by MSKCC, highlighting the potential for antigen escape. Dr. Sadelain expressed his concern for antigen escape, citing the need to find other targets for these patients.
  - Dr. Sadelain indicated that MSKCC has refined its manufacturing process through dose escalation trials, shortening the manufacturing timeline to approximately 9-10 days.
  - Relating to on-target toxicities, Dr. Sadelain did not believe cytokine release was a pre-requisite to tumor response. Patients with low tumor burden that did not experience severe CRS achieved similar CR rates to patients with high tumor burden. Furthermore Dr. Sadelain believes that CRS can be managed without compromising response rates.

- **CAR-T Has an Optimistic Future in Solid Tumors and Lymphomas**. Dr. Sadelain acknowledged that outcomes seen in the CAR studies with CD19-positive ALL have set a high efficacy bar. The current focus is to replicate these results in chronic lymphocytic leukemia (CLL), lymphomas, and solid tumors. Both KOLs believed that adoptive T-cell therapies will be successful in solid tumors.

Dr. Sadelain mentioned that CARs can be further modified to combat the immunosuppressive microenvironment of solid tumors. Memorial Sloan Kettering plans on using an armored CAR targeting the MUC 16 antigen that also secretes the IL-12 cytokine in ovarian cancer.

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